University of Alberta

A Psychobiological Model of Cravings in Substance Dependence: Electrophysiological and Neuropsychological Correlates

by

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DEDICATION

For M.R.R.

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LIST OF ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid, the principle metabolite of 5-HT
5-HT	5-hydroxytryptamine, serotonin
5-HTP	5-hydroxytryptophan, tryptophan, precursor to 5-HT (see also Tryp)
6-OH-DPAT	6-hydroxydopamine, a chemical that destroy DA terminals
7-OH-DPAT	7-hydroxydopamine, a dopamine D2 receptor agonist
AA	Alcoholics Anonymous
ACTH	adrenocorticotrophic hormone
ADHD	Attention Deficit/Hyperactivity Disorder
AHE	Alberta Hospital Edmonton
AIDS	Acquired Immunodeficiency Syndrome
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionatic acid; a glutamate receptor subtype
BAS	behavioural activation system (Gray, 1972)
BIS	behavioural inhibition system (Gray, 1972)
BPI	Basic Personality Inventory (Jackson, 1996)
CCK	cholecystokinin
CDRC	Clinical Diagnostics and Research Centre
CI	confidence interval
CNS	central nervous system
CREB	cAMP response element binding protein, a drug-regulated transcription factor, underlying counteradaptation in the brain
CRF	corticotrophin-releasing factor
CSF	cerebrospinal fluid
CT	computerized tomography

Cz	electrode located over central midline
DA	dopamine
DHEAS	dehydroepiandrosterone sulfate, an adrenal androgen
DHT	5,7-dihydroxytryptamine, a 5-HT neurotoxin
DIS	Disinhibition, one factor of the SSS-V
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DTR	Daily Thought Record
EAS	experimenter-administered stimulation
EEG	electroencephalogram
EGI	Electrical Geodesics Inc., manufacturers of the geodesic sensor net
EOG	electro-occulogram
ERP	event-related (brain) potential
ES	Experience Seeking, one factor of the SSS-V
ΔFosB	a drug-regulated transcription factor underlying sensitization in the brain
FAE	fetal alcohol effects, a milder form of FAS
FAS	fetal alcohol syndrome
fMRI	functional magnetic resonance imaging, based on blood oxygenation level dependent contrast related to changes in local blood flow
Fz	electrode located over frontal midline
GABA	gamma amino butyric acid, the principle inhibitory neurotransmitter in the CNS
GLU	glutamate, the principle excitatory neurotransmitter in the CNS
HPA axis	hypothalamic pituitary adrenal axis
HVA	homovanillic acid, a DA metabolite
ICD	Impulse Control Disorder
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Edition
ICSS	intracranial self-stimulation
ITI	intertrial interval

LH	left hemisphere
LORETA	Low-resolution electromagnetic tomography, a mathematical model used in the computation of electrical sources in the brain, as seen on the scalp
LTP	long-term potentiation, associated with synaptic plasticity; thought to be a neural correlate of learning
M100907	a selective 5-HT$_{2A}$ blocker
MANOVA	multivariate analysis of variance
MAO	monoamine oxidase, an enzyme responsible for breakdown of catecholamines
mCPP	*m*-Chlorophenylpiperazine, a combined 5-HT agonist/antagonist
MEP	motor evoked potential
MMCQ	Multidimensional Multitrait Craving Questionnaire
MMN	mismatch negativity, an ERP waveform thought to reflect differences between auditory standard and deviant tones
MRI	magnetic resonance imaging (see also NMR)
N200	brainwave component, occurs in response to novelty and salience
NA	Narcotics Anonymous, a "12-step" program affiliated with AA
NAcc	nucleus accumbens
NE	norepinephrine; alternately noradrenaline
NIDA	National Institute on Drug Abuse
NMR	nuclear magnetic resonance (imaging; see also MRI)
NS	novelty seeking (see also SS)
ns-SCR	non-specific skin conductance response
OCD	obsessive-compulsive disorder
OCDS	the obsessive-compulsive drinking scale
Oz	electrode located over occipital midline
P300	brainwave component, thought to index "context updating" (see also P3b); less precisely, sometimes used to refer to the family of waveforms including P3b *and* P3a
P3a	brainwave component, occurs in response to unexpectedness
P3b	brainwave component, thought to index "context updating" (see also P300)

PCA	principal components analysis
PET	positron emission tomography
PFC	prefrontal cortex
PKA	cAMP-dependent protein kinase
PTSD	posttraumatic stress disorder
Pz	electrode located over parietal midline
rCBF	regional cerebral blood flow
RH	right hemisphere
RON	reorienting negativity, a brainwave component
SCL	skin conductance level, a tonic measure of sympathetic activity
SCR	skin conductance response, a phasic measure of sympathetic activity
SKF 82958	a dopamine D1 receptor agonist
SN_{pc}	substantia nigra pars compacta
SPECT	Single Photon Emission Computed Tomography
SSRIs	selective serotonin reuptake inhibitors, a class of novel antidepressants
SS	sensation seeking (see also NS)
SSS-V	sensation seeking scale, fifth edition (Zuckerman, 1979)
STG	superior temporal gyrus
TBI	traumatic brain injury
TH	tyrosine hydroxylase, the rate-limiting enzyme in DA production, responsible for conversion of tyrosine to dopa
TPP	tegmental pedunculopontine nucleus
Tryp	tryptophan, precursor to 5-HT (see also 5-HTP)
VTA	ventral tegmental area
WAIS	Wecshler Adult Intelligence Scale, a test of IQ
WCST	Wisconsin Card Sorting Test, a neuropsychological test of frontal lobe function
WHO	World Health Organization

CHAPTER ONE: INTRODUCTION

Cravings in the Context of Addiction and Dependence

Addictive behaviour can be defined as any activity considered excessive, of an appetitive nature, compulsive, and beyond the control of the individual (Davis, 1996b; Otter and Martin, 1996). Addiction is a costly societal problem. 1996 statistics estimated the total cost of substance abuse to Canada's economy as exceeding $18.45 billion, approximately 2.7% of the nation's GDP (Single et al., 1996). Addiction also carries significant social stigma and results in societal and personal crises, including child and spousal abuse, motor vehicle crashes, teen pregnancy and spread of sexually transmitted diseases, school failure, low worker productivity, escalating health care costs, and homelessness, and other disruptions of work and personal life (United States Department of Health and Human Services, 2000). Aside from its direct costs, drug use can be a mode of transmission for many serious infectious diseases including acquired immunodeficiency syndrome (AIDS), tuberculosis, and hepatitis (Leshner, 1997b).

Craving has been defined as an "appetitive urge, like hunger, characterized by withdrawal-like symptoms. Symptoms are elicited by internal and external cues evoking memory of euphoric effects… or discomfort from withdrawal" (National Institute on Alcohol Abuse and Alcoholism, 1989; cited in Potgeiter et al., 1999). They are strongly related to urges, desires, and obsessive thoughts and, as such, constitute a key component of addiction. While the exact relationship between drug craving and drug abuse has not been determined, cravings are reliably characteristic of the dependence phase of addiction. As Anton and Drobes (1998) point out, craving is "a constant companion for the addicted individual". Burton and Tiffany (1997) call it "the most salient, frequent, and troublesome symptoms [smokers] experience over the first month of quitting". At the same time, behavioural manifestations of cravings are considered important features of addiction (Tiffany, 1990), and in some cases it may represent a "formidable obstacle preventing many [addicts] from even attempting to quit" (Burton and Tiffany, 1997) and a "significant barrier to recovery" (Mezinskis et al., 1998). A checklist of criteria necessary for dependence, as determined by the World Health Organization (WHO) in 1981 (Table 1.1) makes clear the predominant and central role of craving. Conversely, Diagnostic and Statistical Manual of Mental Disorder, 4th Edition or *DSM-IV* (American Psychiatric Association, 1994; Table 1.2) criteria have attempted to minimize the role of craving in dependence. To the extent that they are critical to the dependence process, an understanding of the biological underpinnings of craving will be of great importance in the resolution of social and economic issues surrounding addiction.

Controversy Surrounding Craving

Cravings are a widespread psychological phenomenon common to casually-used substances and behaviours (Davis, 1996b; Milkman and Sunderwirth, 1987). However, while the experience of craving is universal, it appears to be *problematic* solely among addicts. This introduces the issue of whether cravings in addiction are qualitatively different (rather than simply more severe) than among casual users. Efforts to distinguish between normal and "pathological" cravings - which culminate in loss of control, a preoccupation with acquiring drugs, and a pattern of relapse over time - are generally absent in theories of craving and compulsive drug use (Miller and Goldsmith, 2001).

Use of the expression by laypeople has led to criticisms that the terminology is imprecise, and may in fact represent multiple related phenomena (Peers, 1996). Among researchers, craving is measured in an assortment of ways (Peers, 1996; Pickens and Johanson, 1992; Wise, 1988): Quantitative measures include speed of consumption (Rankin et al., 1979), weight of waste materials (Hartman et al., 1998, as cited in Mezinskis et al., 2001), forced choice experiments (Kaplan et al., 1983, as cited in Tiffany, 1990), "breaking point", the point at which the number of presses required to obtain a drug overwhelms the attractiveness of the drug (Ciccocioppo, 1999), and subjective measures such as random rating throughout the day (e.g., the Ecological Momentary Assessment; Shiffman, 2000) and, of course, questionnaire measures. There is also significant disagreement as to whether craving should be conceptualized as an extreme urge to use a drug, or whether it should be considered along a spectrum of desire (Goldsmith, 1998; Mezinskis et al., 1998). Most addicts seem to use the word to mean any desire or urge (Modell et al, 1992a). Because craving is a dynamic process, it may have inherently poor test-retest reliability (Mezinskis et al., 2001). In addition, craving tools and questionnaires are generally directed at only one drug, decreasing their comparability (Goldsmith, 2001). Clinically, craving is generally measured only indirectly, if at all[1].

Beyond issues of definition and measurement, there are problems concerning the phenomenological nature of craving. While addicts appear able to distinguish between cravings for different drugs, to quantitatively assess them, and to separate them from other mood states surrounding dependence (Mezinskis et al., 1998), it remains unclear whether the experience of craving is one of desire or dysphoria (Gossop, 1990; Peers, 1996), or whether it is even a conscious process (Berridge and Robinson, 1995; Cepeda-Benito and Tiffany, 1996; Davidson, 2003; Miller and Goldsmith, 2001; Tiffany, 1990, 1999; Tiffany and Carter, 1998). It is also possible these processes differ for different drugs (Gossop, 1990). It is unclear whether craving is described in the same way among active users as those committed to quitting (Warburton, 1990): Some addicts define cravings as “needs”, while others may classify them as “wants” or “likes”. The time course of the craving process is similarly ambiguous, with cravings reported shortly after drug presentation, during active withdrawal, and later preceding relapse. There may be qualitative differences in cravings during these stages (Mezinskis et al., 1998).

More importantly, craving and drug use behaviour appear to be relatively loosely linked (Table 1.3, Shiffman, 2000). It has been argued that craving may be neither sufficient nor necessary in relapse (Mezinskis et al., 2001; Pickens and Johanson, 1992; Tiffany, 1990), although some instruments have shown promise (e.g., Anton and Drobes, 1998; Drobes et al., 1994; Kampman et al., 1998). To the extent that craving does play a role in drug-seeking behaviour, it has been noted that "understanding the factors contributing to the precipitation of relapse constitutes an important step for the development of treatment strategies" (Ahmed and Koob, 1997; Goldsmith, 2001). For instance, polysubstance abusers who report having lost urges for cocaine after aversion treatment have much higher rates of total abstinence than those who report still having urges (90% *vs.* 33%; Frawley and Smith, 1992). In this vein, Anton and Drobes (1998) have suggested that changes in craving level might signal improvement or deterioration in the patient's condition. Accordingly, novel pharmacotherapies such as Zyban, Ibogaine, and the nicotine patch are directed towards a reduction in craving as a therapeutic goal.

Controversy surrounding the topic has existing since the 1950s, when the World Health Organization (WHO) met with the goal of providing a scientific definition of craving. This resulted in a distinction being made between physical and psychological dependence, but no general scientific consensus regarding the usefulness of the term (Mezinskis et al., 2001). Wise and Bozarth (1987) argue that the chief difficulty with dependence explanations is their circularity: They are both caused by and predict drug use. The authors further argue that, in general, dependence theories suffer from explanatory value regarding how addictions begin in naïve individuals, nor why relapse is so common among those in long-term abstinence. Others have questioned whether the term "adds little more than a convenient word for expressing the probability of an individual engaging in drug-taking behavior" (Pickens and Johanson, 1992). As some authors note, the term has shown a "remarkable persistence" (Gossop, 1990) given the confusion surrounding the concept. While such disagreements have led some authors to argue for the use of different words rather than craving (see Gossop, 1990 for a review), the argument is mainly semantic[2], as it is questionable whether addicts themselves would abandon the concept. Use of the term remains widespread although, as Peers (1996) notes, this is "presumably because everyone thinks that they know what it means". As a result, rather than being the subject of rigorous investigation, cravings are treated as curious epiphenomena of the addictive process.

Today, increasing knowledge of the biological foundations of drug addiction has led to renewed interest in craving. Most notably, Robinson and Berridge's (1993) incentive-sensitization theory of addiction, which suggests putative neurobiological correlates for craving in terms of dopamine (DA) release in the nucleus accumbens (NAcc), has generated testable hypotheses in animal models of craving. Moreover, recent advancements in imaging technologies, with recent fMRI (Breiter et al., 1997; Maas et al., 1998) and PET (Volkow et al., 1999) studies of cocaine effects in humans, demonstrate the value of imaging technologies in measuring subjective experiences like craving. Importantly, the 1999 study by Volkow and colleagues found correlations between brain activity and alterations in internal states, suggesting that these were not simply changes related to drug use.

Evolutionary Perspectives on Craving

Some authors argue that addictions result from a drug's "high-jacking" of the brain's normal reward systems (Kelley and Berridge, 2002; Shiffman, 2000). In other words, addictive drugs and behaviours are thought to exploit the neural systems responsible for the rewarding qualities of food, sex, and other endogenous appetitive stimuli. However, food and sexual reproduction share a common feature of being necessary for the survival of the species, whereas habit-forming drugs are not. Hence, it is argued that the neural systems underlying the addictive qualities of various substances and behaviours originally had survival value (Ruden, 1997).

Since these systems play a role in behaviours critical to species survival, it is argued that they have the capacity to shape behaviour, making it automatic and compulsive (Ruden, 1997). It may be reasonable to assume that the longer the behaviour is frustrated, the more likely that cravings will elicit obsessive ruminations and affective responses, and the more likely this instinctive, reflexive behaviour will occur. However, it has been observed that cravings increase even as drug-induced pleasure declines and negative consequences accumulate (Robinson and Berridge, 1993), making a simple "pleasure-seeking" explanation to this question insufficient (Miller and Goldsmith, 2001). Further, it is unclear why some people appear to be more prone to addictive tendencies than others.

Models of Differential Vulnerability

Theories of differential vulnerability explore the range of individual differences in drug use behaviour. Some individuals can safely experiment with drugs with no apparent ill effects, while others experience a loss of control; still others appear to have no urge to experiment (Bigelow et al., 1988). Known demographic risk factors for development of substance abuse include a positive family history, and behavioural problems in childhood (Tarter and Mezzich, 1992). There is also consistent interest in whether certain personality characteristics are predictive of substance abuse or dependence (Badawy, 1996). If cravings play a causal role in drug use initiation or escalation, they are intimately connected to issues of susceptibility.

Theories of vulnerability also have implications for the role of cravings in determining one's "drug of choice". Reasonably, addicts should demonstrate preferences for those drugs that elicit the most severe cravings. Hence, clinically, there is utility and validity in determining whether certain drugs engender the strongest cravings.

Four theoretical models explore differential vulnerability. However, they contradict one another in several ways. These theories argue that addictive qualities are, alternately: intrinsic to the drug; dependent on the interaction of the drug with the individual, or; specific to the individual, given their unique biological makeup. The idea of a common neurobiological substrate underlying all addictive behaviour (i.e., dopamine release in the nucleus accumbens) is the most supported, but still contentious. We review these briefly below.

Drug-Induced Addiction. Alexander (n.d.) has described the concept of drug-induced addiction as the belief that certain drugs swiftly and irrevocably cause catastrophic addictions in individuals who try them. Generally, it reflects the conventional belief that the more dramatic the withdrawal symptoms produced by the drug, the more "dangerous" it is (Leshner, 1997b). As a result, this argument is typically applied to so-called "harder" drugs such as heroin and crack cocaine, although not exclusively so[3].

There are two central tenets of the model: all or most people who use a given drug beyond a certain minimum amount become addicted; and no matter what proportion of users become addicted, their addiction is caused by exposure to the drug. That is, "addictiveness" is understood as a property *intrinsic* to certain drugs (Gossop, 1990).

This theory has little empirical support. Although animals given the ability to self-inject heroin have been shown to do so to their own detriment and to the exclusion of other activities, human patients given patient-controlled analgesia machines for the self-administration of morphine generally do not (Alexander, n.d.). Hence, mere exposure to the drug does not necessarily lead to uncontrolled use. The theory also fails to address that some very addicting drugs do not produce severe physical withdrawal symptoms (e.g., cocaine, methamphetamine). In addition, once debilitating withdrawal symptoms of other drugs (e.g., heroin) can now be effectively managed with medication (Leshner, 1997b). Finally, it fails to explain why some individuals become dependent on relatively innocuous substances, while others experiment relatively safely with harder drugs.

The Self-Medication Hypothesis. Khantzian's (1985) self-medication hypothesis, dictates that "the psychoactive substances people select are not randomly chosen. The substance of choice is a result of an interaction between the psychopharmacological action of the drug and the dominant personality makeup of the person" (Teichman et al., 1989). Proponents note that most addicts express a preference for one drug, a process referred to as "self-selection". One's drug of choice is presumably a reflection of an underlying psychopathology that the individual is attempting to treat.

It is hypothesized that reinforcement results from rapid symptom improvement, while cravings result from a dysphoric return to the baseline psychopathological state. Thus, substance abuse acts via negative reinforcement, removing the aversive underlying state (Bardo et al., 1996). However, the very logic underlying this argument has been questioned: "Even if it is known that a psychiatric disorder has preceded the onset of substance abuse, the mere coexistence of the two disorders does not explain the [underlying] mechanism" (Weiss, 1992).

Of note, self-medication theory predicts the drug effect should *oppose* the pathological internal state of the individual. For instance, an individual who is aggressive should be drawn to drugs with calming effects, such as opiates. While this assumption might appear self-evident, the following theory makes a contradictory prediction.

The Adaptive Model. Milkman and Sunderwirth (1987) attempted to extend the self-medication model to normal populations, on the basis that underlying neurotransmitter levels "represent a continuum from pathology to the normal range" (Netter, Hennig, and Roed, 1996). That is, addicts vary in severity, but not in kind, from nonaddicted individuals. Hence, the adaptive model (Alexander, n.d.) suggests that individuals use drugs to cope with feelings of isolation or alienation.

These theories have in common an emphasis on antecedent behaviours indicating risk for substance abuse (Bardo et al., 1996). However, the types of cravings each would give rise to are at odds: self-medication posits that cravings result as a dysphoric return to an distressing baseline state, whereas the adaptive model suggests that cravings reflect a desire to enhance the baseline state. While the self-medication model maintains that individuals choose drugs which suppress their symptomatology, Milkman and Sunderwirth (1987) argue that individuals choose drugs which *reinforce* their preferred defensive style. That is, individuals with a tendency to behave impulsively are more likely to abuse stimulants, while those who are more introverted are likely to crave depressant drugs. In support, studies of abstinent addicts have found that stimulant abusers are most likely to be impulsive and extraverted, while depressant users are more prone to introversion and anxiety (Rosenthal et al., 1990). Yet questions remain regarding whether the drug causes or relieves the underlying affective state.

Recently, some authors have attempted to reconcile these contradictory views, predicting that, "in some addicts the chain of stress-induced neurochemical and neuroendocrine reactions act as a priming stimulus, increasing craving… [while in others], who are inherently hypoaroused, anhedonic, apathetic and who manifest blunted reactivity of HPA axis, may be seeking [stimulants] for the purpose of self-medication" (Majewska, 2002).

The Common Substrate Hypothesis. Finally, the common substrate hypothesis states that the final common pathway of all drug dependence is DA release in the NAcc, and related functioning of mesocorticolimbic system (Breiter et al., 1997; Kelley and Berridge, 2002; Koob and Nestler, 1997; Nestler, 2001; Robinson and Berridge, 1993; Spanagel and Weiss, 1999). Proponents argue that there is clearly a common biological basis to all craving, mediated by dysfunction of this system, a stance which is supported by the National Institute on Drug Abuse (NIDA, 2000).

Evidence supporting the theory includes the widespread phenomenon of drug replacement among addicts (e.g., when the original drug becomes unavailable) and in animal models (Gorwood et al., 2001); prevalence of polyaddiction (Miller and Gold, 1993); and lack of support for genetic heritability of addiction "type" from one generation to the next (Tarter and Mezzich, 1992). Observations have been made regarding replacement of some impulse control disorders with drugs of abuse, suggesting cross-tolerance (Soutullo et al., 1998). PET scans also generally support the contention of common neural circuitry, showing similar results for a number of different drugs of abuse (Volkow, 1997). This has led some researchers to infer that predisposition to drug abuse represents "the ramification of a generalized behavioral disposition" which may even culminate in behavioural, or "process", addictions (Tarter and Mezzich, 1992). At the very least, some common "comparator" mechanism estimating reward magnitude, determining appropriate choice of behaviour would appear to be necessary (Grigson, 2002).

On the other hand, this theory does not address the matter of individual differences in drug effects, differences in subjective "attractiveness" of one drug over another, nor the fact that attractiveness varies between individuals. Even polydrug users generally report having a "drug of choice", or one drug that is "the problem"; this is particularly vexing in cases where individuals have sampled "harder" drugs before settling on alcohol or nicotine. Some individuals appear to be more sensitive to the discriminative effects of various substances (for a detailed discussion, see Clark, 1990). Grigson (2002) has made the intriguing proposition that the NAcc may be pluripotent, with responses tuned by potentially rewarding events in the environment. Conversely, different genetic predispositions might reasonably lead some individuals to prefer one drug sensation over another (Bardo et al., 1996), although it is also possible that an available drug competes with and inhibits other potential reinforcers (Grigson, 2002). However, the theory also cannot account for changes in drug preference. Nor, as J. Morrison notes, does it explain why individuals might have cravings for different substances at different times (personal communication, October 14, 2003).

Moreover, given its role in personality characteristics such as impulsivity and emotional functioning, the mesolimbic DA system is also thought to play a fundamental role in personality. This has led some authors to suggest that an "addictive personality" may underlie the genetic predisposition for enhanced drug cravings. However, evidence for an addictive personality type remains elusive (Davis, 1996b). In fact, some traits generally associated with vulnerability (e.g., sensation seeking) appear to differ between drug groups (Gorwood et al., 2001).

Negative reinforcement is also difficult to account for via common substrate theory. According to the theory, cravings for different drugs should be interchangeable (Wise, 1988), a claim which current reviews (e.g., Grigson, 2002) generally support. However, studies have failed to confirm that dependence on one drug presupposes dependence to another (Hughes et al., 2000), although some medications aimed at reducing cravings for one drug may work for others (Zickler, 2000). Several lines of evidence serve to illustrate this issue. First, while drugs can substitute for one another in situations of deprivation, they apparently fail to do so when the animal is sated (Nader et al., 1997). At the same time, while DA levels in some brain regions have been shown to predict initiation and rate of morphine self-administration, these behaviours do not correlate with rates of bar pressing for water (Glick et al., 1992). Similarly, rotational behaviour in rats, an index of striatal DA (Denenberg et al, 1978; Giambalvo and Snodgrass, 1978), correlates with increasing patterns of amphetamine self-administration, but *decreasing* patterns of morphine self-administration (Glick and Hinds, 1985). Inductions of GABA, an inhibitory transmitter, into either the dorsal prefrontal cortex or the NAcc core block drug-induced behavioural reinstatement, but not food-induced food-seeking behaviour (McFarland and Kalivas, 2001). Stress, which may act as a reinforcer (Sinha, 2001), has been shown to reinstate responding for drug- but not food-reward (Ahmed and Koob, 1997). Further, the role of adrenal hormones appears necessary for long-term, but not short-term, cross-sensitization between stress and cocaine challenge (Prasad et al., 1998). Moreover, changes in psychostimulant self-administration following alterations in stress hormones do not generalize to other reinforcers, such as food (Marinelli and Piazza, 2002). Finally, some studies have failed to find activation to symbolic reward in critical structures, such as the nucleus accumbens (Knutson et al., 2000). These observations challenge the notion that natural reinforcers, conditioned reinforcers, and drugs are subserved by identical circuitry.

Moreover, because addiction to several drugs suggests higher rates of DA release, the theory predicts that polyaddiction should be associated with more severe outcomes. However, in a study examining concurrent abuse of other drugs in addition to cocaine, McMahon and co-workers (1999) found that duration of concurrent alcohol abuse was related to *decreased* cocaine relapse following treatment. Similarly, Frawley and Smith (1992) reported that polysubstance abuse was related to lower rates of relapse at one-year abstinent than was abuse of single substances.

Finally, it is noteworthy that conventional reinforcers do not tend to be abused or lead to problem behaviours (Heyman, 1996; Warburton, 1990). Further, not all drugs that increase DA levels (e.g., medications for Parkinson's Disease[4]) are typically abused. Nor do all addictive drugs (e.g., the benzodiazepines) clearly activate DA (Warburton, 1990). In addition, chronic effects of different drugs of abuse on the DA system are variable (Pulvirenti and Diana, 2001).

Clearly, there is a need to develop an understanding of the roles of other neurotransmitter systems implicated in mesocorticolimbic functioning (Koob, 1997; Koob and Nestler, 1997; Robbins and Everitt, 1996; Volkow, 1997). This need is underscored by the success of anticraving drugs (e.g., acamprosate and naltrexone) that work on non-DAergic neurochemical systems. In addition, neurotransmitter systems not linked to the acute reinforcing effects of a drug are often altered as a result of chronic administration (Koob and Nestler, 1997). Centrally-acting drugs activate multiple physiological systems, potentially resulting in different pharmacological and hedonic profiles, and, hypothetically, *types* of withdrawal (Clark, 1990; Stewart et al., 1984). However, proponents of the theory argue that these observations should not overshadow the similar subjective states produced by DA activation (Bozarth, 1990).

The Multidimensional Nature of Craving

Possibly, some criticisms of the craving concept reflect the inadequacy of the literature to identify and contend with the multifaceted structure of the concept, with different authors referring to disparate processes when discussing "cravings". Cravings appear to be characterized by three distinct components: Subjective desire; obsessive cognition; and impulsive/compulsive behaviour. Indeed, the different dimensions of the craving concept may in fact have separable, albeit related, neuroanatomical bases; it has been hypothesized that "different neuropharmacological and psychological treatment interventions may be more salient to *various components* of craving" (Anton and Drobes, 1998, italics added). Aside from diminishing the generalizability of their findings, this multidimensionality has also lead to arguments about which description is "right". Clearly, like other subjective constructs, research into craving requires coordinated behavioural, physiological and biochemical, as well as subjective study (Mezinskis et al., 2001; Rankin et al., 1979). Given the criticism surrounding the concept, an obvious question is why these dimensions of dependence have not received more coordinated study. This reflects both methodological problems with comparison between different levels of measurement and, relatedly, difficulties with the generalizability of findings. Some of these difficulties are unique to the study of drug craving, as will be discussed below.

Problems Inherent to the Study of Craving

The first studies of craving were in human subjects. Investigators studying human addiction can directly ask the addict how he was feeling or what he was thinking about immediately preceding drug use. This line of research also allows researchers to examine potentially meaningful behavioural abnormalities seen only in complex human interactions, including correlates of drug use (e.g., peer relations, family background, employment variables) that could not be explored realistically in animals. Survey research gives the added benefits of studying large populations of individuals to determine incidence and prevalence rates. Done longitudinally, it also allows the researcher to track changes in populations over time.

Nonetheless, human studies are faced with certain limitations, particularly in studies of addiction. In the case of craving, the researcher must contend not only with the difficulties of studying a subjective phenomenon (e.g., poor replicability and demand effects), but also in studying a stigmatized behaviour (Leshner, 1997b). Human research is also held to ethical constraints that may limit the ability of the researcher to fully control the experimental parameters. These complexities and ambiguities result in decreased reliability in human studies.

Conceptual models in lab animals have the benefit of greater precision in experimental control; that is, the researcher is better able to control his independent variables in terms of precision in drug doses, the exact nature and magnitude of reinforcers, the behaviours required to obtain the reinforcers, and the contexts under which such stimuli are available. Similarly, there is also greater precision in recording responses. In addition, invasive techniques for providing reward (e.g., intracranial self-stimulation [ICSS], or injection into putative reward areas of the brain) are extremely powerful. A list of the factors shown to affect drug self-administration behaviours is presented in Table 1.4; the reader is referred to Schuster (1990) for a wide-ranging discussion. Finally, animals provide the opportunity for direct histological examination.

However, critics of animal research question both the generalizability and external validity of this research, contending that animal analogues of addiction present imperfect, artificial comparisons to the addictive process. Moreover, anatomical organization and connectivity of the relevant structures may differ between species (Davidson, 2003). Similarly, there is also a potential confound of ecological validity, as the animal does not self-select the experimental environment, as it would in nature[5]. Lastly, critics argue it is difficult, if not impossible, to make inferences regarding the "thoughts" or "feelings" of animal populations, factors which are often considered important motivators of human drug-taking behaviour. So, while animal studies provide good models for the study of addiction, they are also controversial.

In this regard, imaging techniques, such as electroencephalography (EEG), event-related potentials (ERPs), and functional brain imaging including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) may represent the best compromise in the study of addictive disorders. Quantitative by nature, these techniques are relatively free of demand effects, as results are difficult or impossible to alter or counterfeit on behalf of the subject. Further, they have the advantage of allowing the researcher to correlate information regarding cognitive functioning or affective state with measurable brain activity (cf., Breiter et al., 1997; Maas et al., 1998; Volkow et al., 1999). Used in conjunction with neuropsychological measures, which have been established as reflecting neural activity in circumscribed brain regions, and questionnaire measures, which gauge internal subjective states, they can provide the best compromise between reliability and external validity.

Goals and Organization of this Thesis

This dissertation seeks to unite these different standpoints by developing and testing a biopsychological model of craving, using electrophysiological (ERP), neuropsychological, and questionnaire measures. Given the practical and ethical difficulties encountered in the study of addiction, it is hoped that such a model will be of significant value.

The order of the chapters reflects the evolution of this model. The following chapter deals with the neurological data surrounding substance dependence, with attention given to separable affective, cognitive, and behavioural sequelae of addiction, demonstrating how these processes are related via common neurobiological circuitry, suggesting their coordinated measurement may provide an opportunity for indirectly gauging one's risk of craving and relapse. The next chapter presents a novel psychobiological model of craving which strives to explain observed clinical phenomena by uniting evidence from the disparate areas of examination, as well as make diagnostic predictions regarding relapse. The model seeks to examine the multidimensional nature of craving, its relationship to impaired cognitive and affective processing in addiction, and its fundamental role in the behavioural activation. Electrophysiological, subjective, and neuropsychological tests of this model follow, using a novel craving questionnaire, designed to quantify the different dimensions of the construct. Finally, the paper concludes with discussion regarding the findings discussed herein, and ramifications for treatment and prevention strategies.

Summary

While the role of cravings in addiction remains contested, they are a key component of dependence. Clinically, drug and alcohol users often describe a state best described as craving preceding relapse (Sinha and O'Malley, 1999), one which they consider a "central experience" of addiction (Shiffman, 2000). Presumably, then, controlling craving could have important repercussions for drug dependence and relapse (Mezinskis et al, 2001). Clinically-based theories predicting susceptibility to drug abuse and dependence are contradictory, although the biologically-based common-substrate model remains the best supported.

Critics charge that the study of cravings is plagued by inconsistencies in the phenomenon under study. These criticisms expose the multidimensional nature of the concept, including affective, cognitive, and behavioural components. Researchers who are unaware of or unconcerned with this multidimensionality are bound to encounter difficulties in terms of proper specification of the craving concept, and its role in addiction and dependence. A psychobiological model of craving, developed from evidence in the animal literature, and human cognitive and electrophysiological findings, shall be proposed that will attempt to organize these conceptual issues into a cohesive framework.

Criterion	Description
craving/compulsion	This consists of a subjective awareness and/or ruminations regarding the compulsion to take the drug or engage in the behaviour.
increased tolerance	Habituation of the reinforcing effects of the drug, which leads to increased frequency or amount used.
drug-seeking behaviour	The process of obtaining the drug or engaging in the behaviour begins to take on increasing importance, such that it overshadows other concerns in the addict's life.
narrowing of repertoire	The addict's behaviour towards the substance becomes more circumscribed and stereotyped. This includes habits, rituals, and preferences developed by the user. Routinization also appears to play a role in the discomfort of abstinence.
withdrawal symptoms	Discomfort, dysphoria, and distress are experienced when the addict cannot perform the activity habitually. These may last for varying periods, and may include, but are not limited to, the physiological effects the substance.
reinstatement following relapse	Symptoms of withdrawal reappear rapidly following relapse, even after prolonged abstinence.
relief or avoidance of withdrawal symptoms	The addict is drawn to the activity in part to avoid the "agony of abstinence". It has been noted that, once learned as a solution, this manner of coping is difficult to replace (Davis, 1996b). Sometimes this strategy will require the addict to plan ahead for this eventuality, even at the expense of current use.

Table 1.1 Criteria of Dependence: Established by the World Health Organization, 1981.

Criterion	**Description (at least 3 of the following must be present, occurring any time in the same 12 month period)**
tolerance	Defined by either of the following: a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect b) markedly diminished effect with continued use of the same amount of the substance
withdrawal	Manifested by either of the following: a) the characteristic withdrawal syndrome for the substance (refer to criteria sets for Withdrawal from the specific substance) b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
overuse	The substance is often taken in larger amounts or over a longer period than was intended.
usage control	There is a persistent desire or unsuccessful efforts to cut down or control substance use.
time commitment	A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects.
diminishment of other activities	Important social, occupational, or recreational activities are given up or reduced because of substance use.
continued problem use	The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Table 1.2 Criteria of Substance Dependence: Diagnostic and Statistical Manual of Mental Disorders IV.

		Use	
		Yes	***No***
Craving	***Yes***	*Urge-associated Use* Use in the presence of urges. Note that their co-occurrence does not necessarily imply that that use was caused by the craving. Use may temporarily decrease the craving, or may act as a priming stimulus enhancing craving.	*Unfulfilled Craving* Use may fail to result due to substance unavailability, attempts at restraint by the individual, the presence of others, or behaviour may be under the control of other stimuli.
	No	*Use Without Craving* Craving may be denied or go unnoticed. Or, craving may be cued by provocative stimuli (e.g., social pressure, drug cues) automatically, without any conscious awareness of desire to use.	*Unproblematic Abstinence* No factors causing use (e.g., baseline state found in non-users and casual, non-problematic users).

Adapted from Shiffman, 2000

Table 1.3 Relationship between cravings and use behaviours.

	Variables affecting drug self-administration
I.	Reinforcement variables: a) Delay b) Magnitude c) Rate and duration
II.	Antecedent conditions: a) Deprivation b) Satiation
III.	Organismic variables: a) Genotype b) Species c) Sex d) Age
IV.	Current environmental contingencies: a) Schedule of reinforcement b) Extinction
V.	Experimental variables: a) Pharmacological b) Behavioural

Adapted from Schuster (1990)

Table 1.4 Classes of variables shown to affect operant behaviour with reference to drug self-administration.

CHAPTER TWO: CRAVING AND THE MESOCORTICOLIMBIC SYSTEM

The Nature and Function of Mesocorticolimbic Circuitry in Craving

The mesocorticolimbic system is generally considered the foundation of drug dependence. Hence, the chapter proceeds with a detailed discussion of the structure and function of the mesocorticolimbic circuitry, followed by examination of the roles of specific neurotransmitters. Next, drug craving as a model of counteradaptation is presented. Historically, this model has not been grounded in the neuroanatomy, so I attempt to link it to the functional neuroanatomy of the mesocorticolimbic system. Finally, evidence connecting this system with cognitive, affective, and behavioural deficits generally seen in addicts will be presented.

The Mesocorticolimbic System

The mesocorticolimbic system originates in the dopaminergic (DAergic) projections of the ventral tegmental area (VTA), innervating the nucleus accumbens (NAcc) and prefrontal cortex (PFC), as well as the amygdala. This circuitry is thought to be the principle neural substrate responsible for drug reinforcement and hedonic regulation of drive states (Miller and Goldsmith, 2001), and the initiation of reward-guided adaptive behaviour (Heimer, 2003). The VTA also targets striatal (caudate, putamen), limbic (lateral septum, amygdala, and olfactory regions), and paralimbic areas (piriform and entorhinal cortex, and anterior cingulate; Knutson et al., 2000); however, the majority of our discussion will be confined to the VTA, PFC, and NAcc. The neurochemical connections and relative placement of these structures is shown in Figure 2.1.

The NAcc, located in the ventral striatum along with the ventral pallidum and olfactory tubercle (Heimer, 2003) and several thalamic nuclei, receives DAergic input from the VTA (Mega et al., 1997). As well, the NAcc receives both direct and indirect innervation from the PFC: Direct glutamatergic innervation from medial and orbitofrontal cortex (Leyton et al., 2002), and the aforementioned indirect DA release from the VTA, which itself receives monosynaptic glutamatergic innervation by the PFC (Sesack and Pickel, 1992). Hence, both DAergic and glutamatergic terminals synapse on the common spiny neurons of the NAcc (Sesack and Pickel, 1992). While the majority of spines receive glutamatergic inputs, approximately 50% also receive the DAergic input, presumably modulating NAcc output (Robinson and Kolb, 1997). Importantly, glutamate and DA have opposing effects on the target neurons in the NAcc (Carlezon and Wise, 1996), allowing for "fine tuning" of accumbal response. This opposition has been demonstrated via electrical stimulation (Hooks and Kalivas, 1995). As part of the anterior cingulate subcortical circuit, the ventral striatum also receives input from the infracallosal cingulate region (Mega et al., 1997). In addition, it is innervated by regions such as the insular and entorhinal cortex, as well as the temporal pole (Heimer, 2003).

In return, the PFC receives indirect feedback from the NAcc, via inhibitory GABAergic projections back to the VTA (White, 1996) that send tonic DAergic inhibition to the PFC (Cabib et al., 1995; Sesack and Pickel, 1992). This circuitry establishes that conditions affecting the NAcc will have an influence upon PFC function. If this feedback is imperfect, it results in "disinhibit[ed activity of] glutamatergic neurons of the PFC which, in turn, increase the DA activity in the NA[cc]" (Bubser and Koch, 1993), potentially acting as feedforward.

Activity in both the PFC and NAcc also has repercussions for the VTA. Lesions of the NAcc using 6-hydroxydopamine (6-OH-DPAT), which destroys DAergic VTA terminals, attenuate operant responding for drugs of abuse (Nader et al., 1997). Similarly, DA antagonist injections into the NAcc attenuate responding in order to obtain VTA electrical stimulation (Nader et al., 1997). Lastly, via this complex connectivity, the PFC may affect [VTA] DA neurons indirectly through the NAcc, which itself sends an inhibitory GABAergic projection to the VTA (Cornish and Kalivas, 2001). Lesions of the PFC result in decreases in DAergic VTA activity, suggesting that "tonic input from the [PFC] may be necessary for some VTA DA neurons to fire spontaneously" (Shim et al., 1996) in the NAcc. These cortical afferents also appear to mediate burst firing (White, 1996).

Related limbic regions are also likely to play a critical role in addiction. The central nucleus of the amygdala sends projections to the VTA, while the basolateral nucleus sends glutamatergic fibers to the NAcc (Heimer, 2003; Koob, 1997). Mesoamygdaloid neurons are also thought to send DAergic projections to the NAcc, where they have an inhibitory influence (Stevenson et al., 2003). In addition, the amygdala also has reciprocal glutamatergic connections with the medial PFC (Stevenson et al., 2003).

Studies of amphetamine pretreatment in rats show an increase in dendritic length and density in the NAcc, as well as in apical pyramidal cells in layer III of the PFC, suggesting drug effects in this region are experientially-dependent and potentially reflect enduring structural changes (Robinson and Kolb, 1997). In general, the rewarding effects of drugs appear to result from DA release in the NAcc "shell" as opposed to the "core", which appears to be mainly motor related (Di Chiara, 1998; Koob and Nestler, 1997; although see McFarland and Kalivas, 2001). The shell is characterized by high DA D1/D3 and opiate receptor binding (Heimer, 2003). Perhaps not surprisingly, this region also appears to be important in the DA response to novel environments (Rebec et al., 1997). The role of the transition zone between the two (the "shore") is still under investigation, but Rebec and co-workers (1997) have noted prolonged, lower amplitude DA responses in this region in response to novelty.

While it remains unclear whether drugs of abuse stimulate DA transmission in the PFC (Di Chiara, 1998), some authors have found the PFC to support cocaine self-administration, which is blocked by addition of the D2-receptor antagonist sulpiride (Goeders and Smith, 1983). Behavioural activation for ICSS into regions of the mesocorticolimbic circuitry, including the

VTA (e.g. Porrino et al., 1984) and PFC (e.g., Mora and Myers, 1977), resembles behavioural output for more conventional reinforcers (Porrino et al., 1984). Interestingly, a study comparing ICSS and matching experimenter-administered stimulation (EAS) into the VTA demonstrated that both the medial PFC and NAcc showed increased glucose utilization following the former, but not the latter (Porrino et al., 1984), suggesting that these regions play a role in goal-oriented behaviour. Bechara and co-workers (2001) argue that hypofunctioning of the ventromedial PFC is likely a contributing factor to the aetiology of substance abuse.

The central nucleus of the amygdala has been linked with the aversive effects of drug withdrawal (Koob and Nestler, 1997). Additionally, the amygdala may be a region responsible for mediating effects of hypothalamic-pituitary-adrenal (HPA) axis activity, giving it a crucial role in stress-related relapse; for instance, during cocaine binges, levels of corticotrophin-releasing factor (CRF) increase in the central nucleus of the amygdala, and continue to rise once the binge has been terminated (Koob, 1997).

Clearly, alterations in any of the mesocorticolimbic regions necessarily carry implications for the rest of the circuit, as “when GLU or DA is manipulated at one site,” (as via increased DA release in the NAcc) “there are likely to be consequences elsewhere in the circuit” (Iverson, 1995). In other words, if one of these areas is affected, it can no longer provide correct “gain control” appropriate to a reward stimulus. In addition to the role of this system, two other circuits are also implicated in behaviours with consequences for addiction. Dorsolateral prefrontal circuitry is implicated in altered executive functioning including set shifting, mental control, and abstraction (Cummings, 1995), working memory, considering options, and maintaining decision-goals (Krawczyk, 2002). Orbitofrontal-subcortical circuitry is involved in social modulation of behaviour, impulsivity, and obsessive-compulsive aspects of addiction (Cummings, 1995), as well as in making “best-guess” estimations, and perhaps emotional experience of gains and losses (Krawczyk, 2002). These three circuits are connected via short association fibres at the cortical level, and do not exhibit cross connections with one another subcortically (Cummings, 1995).

However, a good deal of evidence suggests that a number of inputs from different regions of the brain have the ability to modify activity in any of these circuits (Heimer, 2003).

DA Function in Drug Reward

The DA hypothesis generally suggests that DA release is the common mechanism by which reward is produced (Bozarth, 1990; Leshner, 1997a; Martin-Soelch et al., 2001). This idea is supported by animal studies demonstrating that drugs of abuse with diverse chemical structures and mechanisms all have in common agonist properties of DA neurons in the NAcc (Nestler, 2001; Richtand et al., 2001). The ability of a stimulus to evoke an arousing response appears to be directly related to DA release in the NAcc (Robinson and Berridge, 1993): DA release in the NAcc has been observed during presentation of water to thirsty rats (Young et al., 1993) and upon presentation of a receptive female to sexually inexperienced rats (Pfaus et al., 1990). Rats will readily press a bar to receive accumbal microinjections of phencyclidine (Carlezon and Wise, 1996) or cocaine (Neisewander et al., 1996), both of which increase accumbal DAergic transmission. Finally, baseline levels of DA metabolites in the NAcc predict initiation and rate of drug self-administration (Glick et al., 1992). In humans, individual variability in stimulant-induced DA release has been noted, and appears to correlate with self-reported "drug wanting" as well as with related traits such as novelty seeking (Leyton et al., 2002).

At the same time, decreased levels of DA are associated with decreased reward effects. DA antagonists appear to attenuate the rewarding properties of reinforcers (Koob and Nestler, 1997), and generate a brief initial increase in responding normally associated with extinction training. Antagonists also block conditioned place preference (Nader et al., 1997), which develops when distinctive environments are paired with rewards. Finally, neurotoxic lesions of the NAcc, its terminal fields, or its DAergic cells of origin impair stimulant self-administration (Wise and Bozarth, 1987). Recently, researchers have argued for the use of DA partial agonists, which bind to the receptor with low intrinsic activity but high affinity, allowing for effective DA neuromodulation: These drugs act as antagonists when DA tone is high, but have agonist properties when tone is low (Pulvirenti and Diana, 2001). The authors note that initial studies show these drugs to reduce the acute reinforcing properties of drugs, but do not appear to be addictive themselves.

D1 and D2 receptors appear to perform opposing functions in the aetiology of addiction. Infusion of D1 vs. D2 receptor antagonists into the entorhinal cortex results in opposite effects in the NAcc (Louilot and Le Moal, 1994). Behaviourally, using a drug reinstatement paradigm in which stable responding for a drug is established and then extinguished, Self (1997) found that a D2 agonist (7-OH-DPAT) induced the behaviour, while a D1 agonist (SKF 82958) produced only weak effects. Furthermore, a priming dose of the D2 receptor enhanced drug-seeking behaviour induced by a small dose of cocaine, while pretreatment with the D1 agonist blocked cocaine's priming effects. He proposed that stimulation of D1 receptors in the NAcc may produce satiety, while stimulation of D2 receptors generates craving. This contention is supported by a number of lines of evidence. D1 antagonism into the NAcc shell or the central nucleus of the amygdala results in increased behavioural activation, presumably as compensation for the loss of DA receptor activity (Koob, 1997). Conversely, the D2 antagonist haloperidol has been reported to decrease self-reported cravings, and increase both perceived and real ability to resist alcohol consumption following a priming dose (Modell et al., 1993; cited in Modell and Mountz, 1995). Studies have shown a dramatic reduction in D2 receptors in cocaine abusers, with regional glucose metabolism scans revealing corresponding decreases in activity in cortical regions receiving DA projections (Volkow, 1993; cited in Volkow, 1997). Also, addicts with higher D2 measures tend to show metabolic increases in response to methylphenidate challenge, while those with lower measures show decreases (Volkow et al., 1999), again suggesting D2 receptors are involved in regulation of reinforcement.

Imaging studies generally support the role of DA release in the mesolimbic structures in subserving reward-related behaviour. Breiter and colleagues (1997) found fMRI signal activation in regions associated with brain reward correlated with reports of both cocaine-induced rush (sudden euphoria) and craving. Similarly, Volkow and co-workers (1999) found increased metabolism to a methylphenidate challenge in the prefrontal and orbitofrontal cortices of individuals for whom mood and craving, respectively, were enhanced. More generally, to examine the effects of lowered catecholamine levels on alcohol self-ingestion, Leyton and co-workers (2000) had women ingest an amino acid mixture designed to lower catecholamine availability and neurotransmission. The authors found decreased ingestion of alcoholic beverages, which tended to correlate with plasma tyrosine concentrations, with no concomitant decreases of ingestion of a control liquid (orange juice); there was no alteration in self-reported "liking" of the ingested alcohol. However, among cocaine addicts, Knoblich and co-workers (1992) found a direct correlation between levels of homovanillic acid (HVA), a DA metabolite, and craving.

However, the DA theory of reward is not without its challenges. Nader and colleagues (1997) discuss several studies that suggest the existence of a DA-independent reward pathway. Indeed, some so-called "hard" drugs, such as inhalants, benzodiapezines, and barbiturates have not consistently been shown to activate midbrain DAergic transmission (Spanagel and Weiss, 1999). And while decreased DA activity appears to be a relatively universal effect of drug withdrawal, the effect of chronic administration of different drugs have more variable effects on DA outflow, including increases in firing rate, decreases in firing rate, changes in burst firing, and even morphological cell changes (Pulvirenti and Diana, 2001). Moreover, unilateral rotation in rats, which appears to index striatal DA levels (Denenberg et al, 1978; Giambalvo and Snodgrass, 1978), has opposite effects on self-administration of morphine and amphetamine, prompting the authors to conclude that, "in contrast to d-amphetamine, morphine reinforcement is due to a decrease rather than an increase in forebrain dopaminergic activity" (Glick and Hinds, 1985). Furthermore, enhanced DAergic activity does not itself inevitably result in rewarding effects (Robbins and Everitt, 1996); in fact, cravings for nicotine have been related to both DA agonists *and* antagonists, although, interestingly, they were associated with different personality profiles

(Reuter and Netter, 2001). Moreover, in studies of normal human controls, relatively high doses of pimozide, a DA antagonist, failed to antagonize euphorigenic effects of *d*-amphetamine, although the two drugs *did* produce opposite mood-regulating effects when given in isolation (Brauer and De Wit, 1997). Most damaging to this theory, knock-out mice that cannot produce DA still show a robust preference for sweet liquids (sucrose and saccharin) over water, a preference which is already established in naïve juveniles (Matson Cannon and Palmiter, 2003).

It is currently unclear what role DA levels subsume (for reviews, see Joseph et al., 2003; Kelley and Berridge, 2002; Wightman and Robinson, 2002). Findings that ICSS, but not matched experimenter administered stimulation, result in different patterns of glucose utilization (Porrino et al., 1984) challenge the assumption that it is reward *per se* that DA activity indexes. Robinson and Berridge (1993) outline several lines of evidence, including the observation that repeated drug self-administrations result in *decreases* in subjective pleasure, mitigating this interpretation. The authors suggest that animal studies confound the difference between this pleasure (i.e., "liking") and drug "wanting", due to the experimental variables observed (Berridge and Robinson, 1995). For instance, facial reactions thought to reflect hedonic assessment of stimuli do not always correlate with behavioural indices of reward. The problem, in the authors' view, is that "changes in wanting look like changes in liking" (Berridge and Robinson, 1995). It has been suggested that different neural mechanisms mediate drug acquisition and maintenance behaviours (Spanagel and Weiss, 1999), or appetitive *vs.* consummatory behaviours (Fibiger, cited in Wickelgren, 1997; Robbins and Everitt, 1996). In fact, the exact role of DA release in respect to the psychopathology of addiction is undecided: "Whether sensitization of mesolimbic dopamine neurons is linked to enhanced rewarding efficacy remains unclear" (Spanagel and Weiss, 1999).

As Joseph and co-workers (2003) note in their review, the role of DA in reward must be considered in light of whether increased release is seen in situations which are not rewarding, or whether preventing DA release necessarily suggests a loss of reward. To this end, Di Chiara (1998) suggests that novelty is a more potent inducer of NAcc DA release than palatability.

Others have linked NAcc activity to salience, as opposed to reward, noting that the defining characteristics of stimuli that activate the region are arousal and unexpectedness (Zink et al., 2003), although DA neurons do appear to respond preferentially to rewards (Wightman and Robinson, 2002). There is also speculation as to whether DA release is related to the conscious experience of pleasure, or acts as a subconscious attentional cue (Berridge and Robinson, 1995; Wickelgren, 1997), perhaps mediating *interest* in obtaining a reward, rather than reward *per se* (Joseph et al., 2003; Leyton et al., 2002). It may, more generally, mediate goal-directed behaviour (Matson Cannon and Palmiter, 2003). A number of other cognitive explanations have also been put forth (Kelley and Berridge, 2002). Some authors have postulated that, given the reliance on *past* DA release in response to a stimulus, DA release "essentially serves as an expectancy mechanism [driving behaviour] without complex intervening cognitions" (Goldman, 1999); this learning hypothesis is supporting by findings that transient DA release is associated with acquisition, but not maintenance, of ICSS (Wightman and Robinson, 2002). It also helps to explain why release has been observed in coping with stressful and aversive stimuli (Joseph et al., 2003). As such, release may serve mainly as coding of an error signal in reward (Schultz et al., 1997), as has been expressed mathematically in temporal difference (TD) models of dopamine action (e.g., Daw 2002; Kakade and Dayan, 2002). Clearly, these hypothesized roles have common elements, and so can be difficult to disentangle (Joseph et al., 2003). Nonetheless, a number of models, discussed below, postulate a pivotal role for DA function in drug dependence.

Dopamine Depletion Hypothesis. The DA depletion hypothesis (Gill et al., 1991) maintains that exposure to a drug causes addiction by disrupting the brain's capacity to produce its own DA stores, necessitating exogenous replacement. While Gill and co-workers did not find evidence of DA depletion in a group of abstinent cocaine addicts, they postulated that addiction may be a downstream result of DA receptor desensitization. In support, McBride and co-workers (1993) demonstrated that alcohol-preferring rats appear to consume alcohol in order to normalize levels of DA activity via behavioural compensation. Also in support, Marchesi and colleagues (1997) found decreased sensitivity in DA-induced prolactin secretion in abstinent alcoholics (Marchesi et al., 1997).

Incentive Sensitization. By far the most influential modern theory of craving, Robinson and Berridge's (1993; reviewed in brief in Berridge and Robinson, 1995) incentive sensitization theory suggests that repeated use of a drug induces persistent neuroadaptation of the system (sensitization of the NAcc), resulting in a pathological increase of the "salience" of the stimulus. It appears as though D3 receptors, which function as post-synaptic receptors in the limbic regions (Goldsmith, 2001), and have a much higher affinity for DA than the other DA receptors, may become downregulated following repeated stimulant exposure, decreasing their "brake" on D1/D2 mediated response, implicating them in DAergic sensitization (Richtand et al., 2001).

Sensitization results in a qualitative change in the individual's reaction to the stimulus, in that the individual "wants" the drug, beyond the point where he still "likes" it, such that "addicts themselves often are bewildered by the intensity and irrationality of their own 'wanting'" (Robinson and Berridge, 1993). Liking is defined as "the immediate evaluation of how pleasurable a stimulus is", while wanting reflects "a process that mediates our attraction toward stimuli in the environment" (Nader et al., 1997). While the two are typically strongly correlated in response to ordinary incentives, it is argued that increases in neural sensitization related to drug wanting decouple the processes in drug addiction (Berridge and Robinson, 1995). That the two processes reflect different states has also been demonstrated experimentally, as treatments shown to reduce the reward value of stimuli (i.e., to decrease approach) seem to have no effect on reactions demonstrating the animal's hedonic response to the stimulus (Nader et al., 1997). That drug administration can occur in the absence of subjective pleasure contrasts with positive reinforcement theories of addiction (Robinson and Berridge, 1993), and the authors note that neither positive nor negative reinforcement theories are sufficient to explain addiction, though this does not preclude their roles in drug-taking. Hence, the stimulus is imbued with "incentive salience", making it "highly salient, attractive and 'wanted'" (Robinson and Berridge, 1993), and capable of eliciting approach, instrumental behaviour, and goal-directed cognition (Berridge and Robinson, 1995). At the point where wanting begins to govern behaviour, the individual experiences pathological craving and loss of control, despite negative consequences surrounding the use of the drug.

Robinson and Berridge (1993) argue that a small, priming dose of the addictive substance reinstates drug use via activation of incentive sensitization. They argue that it is the common neural circuitry of mesocorticolimbic DA sensitization that enables doses of one drug to prime for administration of other drugs. By the same token, drug-associated stimuli are imbued with increased salience, culminating in relapse. "Pathological enhancement" (Ciccocioppo, 1999) of DA release to cues that signal the reinforcer occurs via associative conditioning. Hence, the authors predict that the only effective drug in addiction will be one that reverses associative processes of neural sensitization (Berridge and Robinson, 1995). Of course, given that they argue the same processes govern "the motivational value of ordinary incentives" (Berridge and Robinson, 1995), it is unclear how such a drug would impact the (presumably adaptive) salience of non-drug stimuli.

Stockwell (1990), however, notes that the idea of incentive cue sensitization is actually incompatible with the process of neuroadaptation. He asks, "why should animals work to get access to cues that are signals of drugs that they find reinforcing if their effects are opposite to the drugs?" (Stockwell, 1990). In fact, not all studies have supported the idea of cue-induced relapse. Ehrman and colleagues (1998) found that, among outpatient cocaine addicts, exposure to auditory, videotaped, and task cues did not elicit higher rates of relapse than did a series of control tasks. Similarly, Dols and co-workers (2002) found that it was context (governing whether smoking was allowed or not), rather than cues, that predicted self-reported craving; cues produced no effect at all in contexts where the behaviour was not allowed. Finally, Koob

(Roundtable discussion, 1997) notes that environmental variables produce a more robust relapse response than those obtained with cue presentation. These observations call into question whether sensitization fully explains the cue-induced drug use phenomenon.

Psychomotor Stimulant Theory of Addiction. The psychomotor stimulant theory (Wise and Bozarth, 1987; Wise, 1988) bears mechanistic, if not conceptual, similarities to the theory of incentive salience. Like Robinson and Berridge (1993), the authors suggest that the psychomotor stimulant properties of all drugs are generated via their activation of VTA DAergic neurons. However, Robinson and Berridge (1993) argue that the psychomotor stimulant and incentive sensitization properties of drugs are dissociable. The authors maintain that a behavioural measure, psychomotor activation, represents a "common denominator" of addictive drugs, arguing that "any event that elicits approach of forward locomotion will serve as a positive reinforcers… approach behaviors and positive reinforcement are homologous" (Wise and Bozarth, 1987). Hence, it is the psychomotor stimulant properties of drugs that determine their positive reinforcing qualities (Wise, 1988). This appears to be true even for depressant drugs, such as opiates and barbiturates, which have biphasic activation profiles, showing behavioural stimulation only at low doses (Gray, 1972). The theory predicts that strength of the psychomotor stimulation should predict the reinforcing potential of the drug, although the authors admit that this proposition is difficult to test as it requires isolation of any interfering side effects. Further, the conditioned psychomotor stimulant effects apparently can be maintained without the support of the DA system for some time (Wize and Bozarth, 1987).

Wise argues that "positive and negative reinforcers can be distinguished empirically on the basis on which parts of the brain they activate" (Wise, 1988). He notes that, while withdrawal appears to be mediated (in part) by neurons in the periaqueductal grey matter *for opiates*, it is clear that different drugs "establish different dependence syndromes and thus relieve different withdrawal symptoms" (Wise, 1988). Hence, treatment for drugs like cocaine, which elicit few classical withdrawal symptoms, and must focus on the positive reinforcing actions of the drug, will be fundamentally different than those treatments dealing with independent mechanisms of negative reinforcement. However, common sense suggests that positive and negative reinforcement comprise endpoints on a continuum: It is not uncommon for negative reinforcement effects (i.e., analgesia) to be replaced by euphoria in longterm patients. Similarly, dependent users tend to find decreases in pleasure associated with drug-taking. Hence, the level of reinforcement may systematically change from one end of the scale to the other. It is difficult to reconcile these observations with Wise's (1988) stance that these processes are governed via recruitment of different neural systems.

Similarly, while the argument the authors make depends on the ability of positive reinforcers to elicit forward locomotion, it is not clear that negative reinforcers cannot do the same thing (e.g., an individual will approach morphine for pain relief); at the same time, at the point of satiety or nausea, an individual may fail to approach a drug.

Finally, Wise and Bozarth (1987) argue that even depressant drugs (at certain doses) are inherently psychomotor stimulating; yet their withdrawal is *also* associated with behavioural activation. This runs counter principles of drug tolerance that withdrawal symptoms generally oppose the positive effects of the drug. These lines of evidence suggest that induction of psychomotor activation might not fully explain the phenomenon of addiction.

Nondeprived/Deprived Model. The nondeprived/deprived model (Nader et al., 1997; Nader and van der Kooy, 1997) suggests the existence of two separate neurobiological reward systems, based on whether an animal is deprived or naïve/sated. Using a conditioned place preference paradigm, the authors demonstrated that bilateral tegmental pedunculopontine nucleus (TPP) lesions block reward in naïve/sated animals, but not when the animal is in withdrawal (Nader and van der Kooy, 1997). Hence, the authors suggest that the TPP has a role in "mediating the motivational effects of stimuli only when animals are in a nondeprived state" (Nader et al., 1997), and suggest a putative role for 5-HT and CCK. Conversely, the authors argue, DA appears to govern reward properties of stimuli only when the animal is in a state of deprivation, as pretreatment injections of α-flupentixol (a D1/D2 receptor antagonist) are only effective in blocking conditioned place preference when the animal is in withdrawal (Nader and van der Kooy, 1997). Hence, the nondeprived/deprived model suggests that, when sated, the TPP-mediated pathway determines motivational value, while in deprived animals this value is DA-dependent and relies on interoceptive discriminative cues to determine the correct choice of reinforcer (Nader et al., 1997).

The authors note that although their model, like that of incentive salience (which proposes separate liking and wanting systems) proposes a dual model of craving, there are some differences. One important distinction is that both liking and wanting can be concurrently activated, while deprivation and nondeprivation are, by definition, opposing states (Nader et al., 1997). They also argue that, since "liking" (as compared to wanting) does not appear to generate approach behaviour, it may be better thought of as a discriminative sensory property of the stimulus. In support, they cite a number of studies showing that the motivational and discriminative properties of stimuli can in fact be dissociated.

It should be noted, however, that most of the authors' experiments investigate the reinforcing properties of either food or opiate reward. These substances may be under joint behavioural control, as nondeprived rats receiving large doses or morphine learn to bar press for food rewards (Kumar et al., 1990), but may differ from psychostimulant drugs (Glick and Hinds, 1985; Nader et al., 1997). Reward for these substances may be more related to the functioning of the endogenous opiate system (Catafau et al., 1999; Kelley and Berridge, 2002), which will not be discussed in detail herein.

Associative Conditioning and Motivational Learning. Growing evidence suggests that DA is crucial to the formation of associations between environmental stimuli and endogenous rewards/punishments, enabling the organism to learn to recognize stimulus relationships (Spanagel and Weiss, 1999). Hence, it has been suggested that DA neurons have an important role in stimulus-reward associations (Hollerman and Schultz, 1998; Schultz et al., 1997, 2000), with DA afferents mediating the attribution of value to conditioned stimuli that signal unconditioned reward (Nader et al., 1997). Specifically, changes in the response rates of individual DA neurons reflect the progress of learning stimulus-reward pairings, with responses diminishing progressively as associations are learned (Hollerman and Schultz, 1998).

To this end, Di Chiara's (1998) motivational learning hypothesis speculates that DA release in the NAcc shell in response to a novel event (Rebec et al., 1997) facilitates the association between its affective properties and the discriminative properties of the stimulus. He notes that this distinguishes his theory from that of Robinson and Berridge (1993), as they do not claim that DA release is involved in the acquisition phase of learning an association. He further posits that drugs, unlike conventional reinforcers, do not demonstrate habituation in this region. It is possible that DA cells in the ventral striatum act to draw attention to significant or surprising events (Wickelgren, 1997); alternately, they may provide internal "representations" of the goal or reinforcer (Robbins and Everitt, 1996). Others have postulated the existence of mechanisms by which the organism automatically generates behaviour based on discrepancies between the present state of the world and its internal representation, with the discrepancy thought to result in an aversive affective state (Karli, 1989).

Serotonin (5-HT) Function in Drug Reward

5-HT neurons in the median and dorsal raphé nuclei project to cortical areas in the forebrain, as well as mesolimbic structures including the NAcc, VTA, and amygdala (Ciccocioppo, 1999; Cummings, 1995). Specifically, 5-HT1A/5-HT3 receptor subtypes predominate in the limbic belt, while the 5-HT2 receptor is found mainly in neocortical regions (Mega et al., 1997). Functioning of 5-HT systems in the CNS has a role in mesocorticolimbic DA performance, in that "suboptimal 5-HT innervation in the central nervous system prevents the VTA and other limbic structures from operating normally" (Bonner, 1996). An oppositional effect of the two neurotransmitters has also been proposed (Daw et al., 2002).

In a review of 5-HT reuptake inhibitors in alcoholism, Thomas (1991) notes a number of lines of evidence suggesting that 5-HT is implicated in addiction (alcoholism), including lowered CSF and urinary levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in abstinent alcoholics, correlations of this compound with both severity of dependence and relapse, and *post mortem* studies showing lower 5-HT and 5-HIAA concentrations in the hippocampus and hypothalamus of alcoholics. Linnoila and Virkkunen (1992) propose a model for "low serotonin syndrome" in addiction due to a deficit in 5-HT activity at the level of the raphé nuclei, characterized by heightened impulsivity, aggression, dysphoria, sleep disturbance, and impaired glucose metabolism. They speculate that these factors result in, and are in turn aggravated by, alcohol (and presumably drug) abuse. They base this hypothesis on evidence suggesting lowered CSF concentrations of the 5-HT metabolite 5-HIAA in various impulse control disorders, including type II (early-onset) alcoholism, arguing that these levels reflect rates of 5-HT turnover in the frontal cortex. In support, a PET study using the combined 5-HT agonist/antagonist *m*-Chlorophenylpiperazine (mCPP) demonstrated that a 5-HTergic challenge activates orbital and prefrontal cortices, as well as regions of the NAcc, thalamus, and caudate nucleus in normal controls, responses that were attenuated or absent in alcoholics (Hommer et al., 1997). The use of selective serotonin reuptake inhibitors (SSRIs) in addiction has been primarily investigated in four areas: Drive reduction, detoxification, treatment of secondary psychopathologies, and neuroprotection (Thomas, 1991).

Central 5-HT levels are determined by tryptophan concentration, because the rate-limiting enzyme of the pathway, tryptophan hydroxylase, is unsaturated with the tryptophan substrate (Badawy et al., 1989; Young and Leyton, 2002). However, some evidence suggests that reduced 5-HT levels may reflect increases in enzyme activity (Cowen, 2002). One study reported enhanced levels of the liver enzyme tryptophan pyrrolase in alcohol-preferring mice, resulting in lower than normal levels of central tryptophan and, presumably, reduced 5-HT levels (Badawy et al., 1989). Less directly, population genetics analyses show that the single common gene GTS, a mutation of tryptophan disoxygenase, occurs in the neighborhood of 15-25% of individuals, a proportion roughly equivalent to that of early onset alcoholics. It is thought that this mutation would "cause elevated levels of the enzyme and a resultant reduction in circulating tryptophan" (Bonner, 1996).

These observations imply that tryptophan concentration, brain synthesis of 5-HT, and enzyme activity may all act as a potential defects contributing to the development and maintenance of addiction. In support of this proposition, Ciccocioppo (1999) notes that both tryptophan and the SSRIs have been shown to reduce administration of amphetamine, morphine, and cocaine. Studies generally show an efficacy level of these drugs between 30% to 50%, with a clear dose relationship (Thomas, 1991). While one might be tempted to attribute this efficacy to reduced levels of depression, reduced intake actually occurs much faster than the related antidepressant effects, and not all studies have found a correlation between the two (Ciccocioppo, 1999).

As is the case for DA, the exact nature of the role of 5-HT in addiction is not clear. 5-HT has been implicated in harm avoidance, thought to reflect a heritable tendency to "avoid punishment, non-reward, and novelty" (Peirson et al., 1999). These authors found strong correlations between harm avoidance and increased 5-HT receptor sensitivity, purportedly reflecting low central basal levels of 5-HT. Van Gestel and colleagues (2002) found that harm avoidance was linked to 5-HT transporter gene insertions, while the 10-repeat allele of the DA transporter gene was overrepresented in individuals with high scores in novelty seeking. These studies would seem to suggest that 5-HT is related to a Gray's (1972) behavioural inhibition system (Daw et al., 2002). Conversely, a large sample of African Americans with cocaine dependence failed to uncover a relationship to polymorphisms of the 5-HT transporter gene

(Patkar et al., 2002), nor was there any association between the genotype and any measure of drug use. However, methodological differences between these studies may preclude direct comparisons.

Alternatively, Wogar and co-workers (1991) speculate that the role of 5-HT is to limit the "value" of reinforcement. In support, the authors found that damage to central 5-HT pathways by injections of the neurotoxin 5,7-dihydroxytryptamine (resulting in levels of 5-HT and 5-HIAA being only 20% of those in the control group) resulted in an increase of the value of the reinforcer. There were no effects of the lesion on DA concentrations. Furthermore, males with alcoholic fathers have been shown to have lower mean cerebrospinal fluid (CSF) concentrations of 5-HIAA, but no difference in levels of DA metabolite homovanillic acid (HVA; Linnoila et al., 1989). These lines of evidence suggest that, in the absence of damage to the DA system, an individual with lowered 5-HT levels must work harder to obtain the same level of reinforcement.

However, direct measures of platelet 5-HT content have provided more ambiguous results (Schmidt et al., 1997). While levels were attenuated in currently drinking alcoholics, they were actually *elevated* in opiate addicts. Both these levels began to approximate normal following short-term abstinence. Further, cigarette smoking appeared to have a normalizing effect in alcoholics (it could not be measured in opiate addicts, as all subjects were smokers).

In addition, a review of the role of 5-HT in addiction (Thomas, 1991) noted that there are shortcomings in preliminary clinical trials of SSRIs, including low numbers of subjects, inadequate follow-up terms, and poor choice of subject populations. Further, the author notes that some studies have suggested that tolerance to these medications begins to develop within a few weeks, suggesting they may not represent a good long-term solution in dependence. The role of 5-HT in addiction is likely far more complicated than is currently understood.

Two models posit a dysregulation between 5-HT and DA in craving. These are reviewed below.

Biobalance Theory. Ruden's (1997) biobalance theory suggests that cravings result from an incorrect proportion of DA to 5-HT. This theory most strongly reflects temperament theories that suggest that novelty seeking is related to DA function, while harm avoidance is related to 5-HT function (Cloninger, 1988).

Ruden's premise is that goal-directed behaviour is associated with increases in DA, via increased arousal and a mechanism of heightened salience, not unlike that proposed by Robinson and Berridge (1993). At the same time, 5-HT constrains the actions of DA by generating a state of satiation, and by constraining sensory input. If the NAcc remains sensitized for too long, a time-dependent decrease in 5-HT follows. When 5-HT levels are too low, the subjective level of salience in the environment overwhelms the animal, and behaviour becomes aimless. Hence, in the biobalance model, it is the equilibrium between the two neurotransmitters that results in optimal information processing. The goal-driven state associated with high levels of DA and concomitant low levels of 5-HT results in the characteristic aimlessness and obsessionality associated with cravings.

In addition, Ruden also suggests that stress plays an important role in the craving process. He suggests that glucocorticoids increase the sensitivity of the NAcc to DA release, such that anxiety-provoking stimuli elicit increased salience. He argues that prolonged stress results in heightened baseline glucocorticoid release, and so sensitizes the NAcc. Once the NAcc is sensitized, the animal remains in a state of heightened alertness.

Ruden is not entirely clear on the association between DA and 5-HT; while the above generally characterizes his views, at some points in his examination he associates craving with both high *and* low 5-HT function. This is, however, in keeping with conflicting studies reporting that novelty seeking and harm avoidance are negatively correlated in normal controls, but positively correlated in substance abusers (Berman et al., 2002).

Two-Stage Process of Craving. Ciccocioppo (1999) presents a model of craving in which DA incentive sensitization is followed by decreased levels of 5-HT, leading to loss of control (see Figure 2.2). While Ciccocioppo's model bears similarities to that of Ruden, it differs mainly in terms of the temporal relationship it posits between DA and 5-HT release. In the first stage, attribution to an external stimulus results in increases in DA sensitization (cf. Robinson and Berridge, 1993). In the second stage, via impulse control mechanisms, 5-HT impels the behaviour of the individual towards the stimulus. Hence, he posits a special role for 5-HT in relapse.

Also in contrast to the model presented by Ruden (1997), Ciccocioppo (1999) does not discuss stress as a factor in craving or relapse.

Dopamine-Glutamate Interactions in Drug Reward

Interactions between DA and glutamate appear critical in the neurophysiology of addiction. Glutamate enhances DA function by increasing levels of DA neurotransmission (Pulvirenti and Diana, 2001), an effect that appears to be independent of DA cell firing rates (Joseph et al., 2003). A recent study demonstrated that DA antagonist administration into the dorsal PFC prevented cocaine-induced drug-seeking reinstatement, as did GABA agonist administration into the VTA; however, reinstatement was rescued by direct DA administration to the PFC, which was sufficient to cause behavioural activation *in the absence of* the priming dose of cocaine (McFarland and Kalivas, 2001). Generalized motoric effects were ruled out. These results suggest that the DAergic projection from the VTA to the PFC, resulting in glutamatergic outflow to the NAcc, is the "initial step" in drug-primed relapse.

Two models discuss the relationship between DA and glutamate in drug use.

Glutamatergic PFC Outflow and Relapse. Kalivas' group (Cornish and Kalivas, 2000, 2001; Kalivas et al., 1998) argues that the initial administrations of a (stimulant) drug result, as expected, in increased DAergic transmission in the NAcc; however, as the stimulus becomes paired with environmental contextual cues, those cues generate craving and relapse via increased cortical glutamatergic drive to the NAcc (Cornish and Kalivas, 2001; Figure 2.3). The authors point to the importance of glutamate release suggested by context-dependent AMPA receptor sensitization, and to the ability of accumbal AMPA to produce locomotion in cocaine sensitized animals *independent* of DA release in the NAcc. The authors also point to the lack of effective DAergic pharmacotherapies for addiction as supporting evidence of the importance of other neurotransmitters, particularly glutamate, in relapse (Cornish & Kalivas, 2000).

While previous versions of their model (e.g., Kalivas et al., 1998) are generally concordant with the one presented in Figure 2.3, there are a couple of notable discrepancies. In the earlier version, the authors suggested that following repeated cocaine administrations, increased glutamatergic drive (from the PFC) on the VTA results in increased DA release in the NAcc, but concomitant decreased DA feedback to the PFC. The later version of the model does not make predictions regarding VTA-PFC interactions. More importantly, in the earlier version, the authors espoused enhanced DAergic drive on the NAcc from the VTA in relapse, while in the new version it is decreased. It is here that this model appears to be at odds with Robinson and Berridge's (1993) incentive sensitization model, as the former concludes that DA is associated with drug responsiveness, which is actually *decreased* following chronic exposure; sensitization, conversely, is based on increased glutamate release (Kalivas et al., 1998).

Glutamatergic Induction of Synaptic Plasticity. Pulvirenti and Diana (2001) take the argument a step farther, and argue that glutamate release results in long-term potentiation (LTP)-like changes in the NAcc and VTA. The authors point to the role of the excitatory amino acids in the modulation of behavioural consequences following exposure to psychostimulants. They note that *in vitro* and *in vivo* studies demonstrate that tetanic stimulation of afferent fibers in the NAcc produces synaptic enhancement, seemingly mediated by ionotropic glutamate receptors; the authors argue that sensitization seen in drug dependence may in fact be a correlate of this LTP.

They also note the role of nitric oxide, which has been shown to be involved in LTP, in the release of DA from the NAcc (Ohno and Watanabe, 1995; cited in Pulvirenti and Diana, 2001) while L-NAME, a nitric oxide synthase inhibitor, appears to reduce the increases in responding typically seen in extinction from cocaine (Orsini, Koob, and Pulvirenti, unpublished observations; cited in Pulvirenti and Diana, 2001). In other words, the authors argue that, "drug sensitization can therefore be viewed as the behavioral manifestation of a form of drug-induced neural plasticity" (Pulvirenti and Diana, 2001) governed by glutamatergic NMDA activity. This plasticity appears to be reliant on D1 receptor systems (Kelley and Berridge, 2002). Others have also argued for the notion of dependence as drug-induced plasticity, albeit utilizing different neuronal mechanisms (e.g., Grigson, 2002; Nestler, 2001).

Indirect evidence for LTP-like changes in addiction includes the fact that NMDA antagonism prevents both the development of morphine tolerance and withdrawal, as well as psychostimulant-induced behavioural sensitization. The authors also point to the known role of ethanol as an NMDA inhibitor, and argue that increased glutamate activity may govern the behavioural hyperexcitability seen during withdrawal from alcohol.

In addition to the role of the PFC, Pulvirenti and Diana (2001) also note that glutamatergic input from the amygdala likely plays a role in the addictive process, as lesions disrupt conditioned responding for both food and sexual reinforcement. Hence, the authors argue that amygdalar output to the NAcc is capable of reinstating responses to reinforcers, also via glutamatergic transmission. In this light it is noteworthy, as shall be discussed later, that similar NMDA-dependent mechanisms have been proposed for lasting sensitization of the stress response (Adamec et al., 2001).

Cellular Basis for Craving: Affective Contrast and Counteradaptation

Stimulus "salience" is a major consideration in most of the above theories. According to Derryberry and Tucker (1994), salient stimuli - those capable of attracting, orienting, or holding attention - tend to be intense, affectively valenced, high in incentive value (i.e., emotional in nature); abrupt in onset (i.e., unexpected); or novel. Initial exposure to salient stimuli, in vulnerable individuals at least, appears to be particularly reinforcing. This may be because drugs differ from natural reinforcers in that they, "can activate reinforcement mechanisms centrally, saturating receptor mechanisms that may never be saturated as a consequence of natural reinforcement" (Wise, 1988).

However, the strength of these initial encounters is counteracted by "enzymatic changes in the brain that counter the desired rise in neurotransmission" (Milkman and Sunderwirth, 1987). Thus, chronic administration of a drug results in increases in the reward threshold, reflecting a decrease in the rewarding properties of the drug (Koob and Nestler, 1997). Accordingly, Solomon and Corbit's (1974; Solomon, 1991) Affective Contrast model proposed that any salient affective experience, positive or negative, is followed by a compensatory after-effect in the opposing direction (Figure 2.4a). In other words, drug administration results in activation of a homeostatic mechanism that opposes the drug effect (Davis, 1996b), explaining why withdrawal symptoms are opposite in nature to the drug effect (Wise, 1988). With repeated administrations, the aversive process increases in strength, eventually overtaking the positive effects of the drug (Figure 2.4b), potentially an operational definition of tolerance or habituation. Koob (1997) notes that this process is common to all major drugs of abuse, and compares it to a change in hedonic "set point". Over time, as the opposing process increases in efficiency, the individual *requires* the drug to maintain homeostasis; thus, without it, he does not feel "normal".

With increased predictability of drug onset, the compensatory system becomes more efficient, such that predictive cues result in the oppositional reaction. Hence, in the absence of the original positive affective response, the dysphoric response occurs when the drug is anticipated: as Siegel et al. (1982) noted, "anticipatory responses attenuate the drug effects and contribute to tolerance". In other words, when the drug is *expected*, the opposing response occurs *in anticipation;* it is this deprivation state that might be conceived of as craving. Thus, anticipation of drug onset becomes a critical component of the craving and the addictive process. Amsel's frustration effect (Amsel and Roussel, 1952), also hinted at this link between expectancy and negative affect[6]. That is, cues originally paired with highly valued rewards now elicit frustration, making them ambiguous and inducing "an approach-avoidance conflict" (Papini, 2003). Reward omissions are associated with increased behavioural drive (including general activity, aggressive responses, excessive drinking, vocalizations, and odor emissions in rodents; Dudley and Papini, 1997) as a result of increased arousal. This behavioural activation is therefore an attempt to escape the induced deprivation state.

Shultz and co-workers (1997, 2000; Hollerman and Schultz, 1998) demonstrated the oppositional effect at the level of the single cell. Using learned sugar reward in monkeys, the authors demonstrated that DAergic projections are at first responsive to reward, then to a cue paired with the reward. When this cue occurs *in the absence of a predicted reward*, there is a *negative* response - i.e., firing drops below baseline levels in anticipation of the reward (Figure 2.5). The last point is most important to the notion of counteradaptation: In situations where a positive affective state is anticipated but not achieved, there is a drop in the firing rate. Reward-dependent responses have been confirmed in both the ventral striatum, and the orbitofrontal cortex (Schultz et al., 2000), although the role in the structures was subtly different. Striatal activity was related to preparation and execution of reward-motivated movements, while the orbitofrontal sites, in addition to predicting reward, were capable of discriminating rewards, and ranking preference of rewards in terms of increased firing rates. Notably, some orbitofrontal neurons responded to reward only when it occurred outside the task constraints; i.e., unpredictably, suggesting they "code an error in reward prediction" (Schultz et al., 2000); hence, responses in this region seem to depend specifically on reward unpredictability (Schultz, 2002). The importance of unpredictability in the DA system was also demonstrated by Besson and Louilot (1997), who reported increased release in the dorsal striatum (which receives innervation from the ventro-orbital prefrontal cortex) when the animal received an expected reward, and decreased release when the animal expected an aversive stimulus.

If this anticipatory oppositional effect can be regarded as craving or withdrawal, it provides some explanation as to how drug cues trigger relapse. Cue exposure triggers the dysphoric anticipatory response, which is experienced as a deficit state. While it has been suggested that no deprivation state is necessary for drugs to function as effective reinforcers (Stewart et al., 1984), anticipation of stimulus onset triggers a *de facto* deprivation state. Spanagel and Weiss (1999) suggest that DA neurons might be involved in the generation of "deficit states that enhance vulnerability to drug craving and relapse". However, symptoms surrounding this deficit state are transient, and should be considered separately from withdrawal *per se*; they may be more aptly thought of as drug "preparation symptoms" (Siegel et al., 1987). These oppositional processes are critical in abstinence, as "when the drug is discontinued these adaptive processes are left unopposed" (Ciccocioppo, 1999), resulting in psychological withdrawal. Studies of placebo effects, "the individual's psychological and physiological response to [an] inactive treatment" (Flaten and Blumenthal, 1999; for a review see de la Fuente-Fernández et al., 2002), have been used to directly examine the role of anticipation in the drug craving. Blumenthal describes the experimental manipulation as follows: "giving people what they think is a drug, but no drug is administered, shows us the effect of expectancy and conditioning, or the placebo effect… [Whereas] if a drug is expected but not given, the body will often react by activating compensatory mechanisms to counteract the expected effect of the drug... This will move the response in the direction opposite of the drug effect." (personal communication, July 18, 2002). This effect may differ between healthy individuals and those in withdrawal, as the normal subject expects the placebo to alter his baseline state, rather than restoring normal function (Flaten & Blumenthal, 1999). That is, deprived individuals presumably use a drug in order to abolish symptoms of withdrawal, while the effect of the same drug on non-addicted individuals is to move them away from homeostasis.

The importance of prediction in the drug process was demonstrated by Siegel and co-workers (1982). The authors trained two groups of rats with heroin injections in a one environment, and vehicle injections in a different environment (i.e., counterbalanced between the homecage and a distinctive room) on alternate days. Over time, they gave the rats increasing doses, inducing tolerance. Following this training procedure, the two groups, plus a control group, received very large doses of heroin. Compared to the control group, which showed almost complete mortality, about two-thirds of the animals receiving the overdose in the environment that had been paired with vehicle died, while only one-third of rats receiving the injection in the room paired with heroin died (Figure 2.6). In other words, the authors were able to demonstrate that animals receiving large drug doses in an environment in which they were conditioned to *expect* drugs had higher survival rates than animals not expecting the drug. This illustrates that cues are fundamental to the drug experience, and that the expectation had an impact on the animal's response to the drug. The findings also illustrate another crucial point. If the response of the animals in the conditioned environment is analogous to a 'craving' situation, as suggested by the work of both Solomon and Shultz's groups, then craving has a fundamentally *protective* quality, allowing the animal to compensate for predicted drug episodes. Hence, despite inherent negative behavioural consequences, craving could serve an evolutionary function.

Following prolonged abstinence, the addict is faced with additional problems. Once the oppositional responses have resolved, drug use once again results in a (relatively-unopposed) positive affective process. As Tiffany (1990) notes, "the addict attempting abstinence has to learn to inhibit automatized actions that would be reinforced if they were enacted."

These studies give us a model of craving, incorporating concepts such as tolerance and habituation. However, to be a useful model, the necessary physiological constituents must be in place. We turn to this discussion next.

The Role of the Mesocorticolimbic DA System in Counteradaptation

The relationship of the mesocorticolimbic system and neuroadaptation *per se* requires elaboration. Miller and Goldsmith (2001) detail counteradaptation effects following prolonged exposure to drugs of reward. These changes include decreases in both DAergic and 5-HTergic neurotransmission in the NAcc in conditions of compulsive use, and increased glutamatergic transmission during withdrawal. Similarly, Cornish and Kalivas, (2001) suggest that initial (novel) administrations of a drug result in increased DAergic action in the NAcc, while in addiction behavioural activation is governed by glutamatergic release from the PFC.

The exact nature of the oppositional effects in the mesocorticolimbic system is unclear. Mechanisms thought to underlie counteradaptation fall into a distinct category of tolerance, known as 'oppositional' adaptation; 'decremental' adaptation on the other hand, has been linked with non-associative conditioning (Cox and Tiffany, 1997) and is a process in which the cell responds to the drug by decreasing its effect via reduced receptor affinity or increased clearance of the drug (Littleton and Harper, 1990). This process has a shorter time-course and bears few implications for the animal in the absence of the drug (Littleton and Harper, 1990). Oppositional adaptation is a longer-lasting mechanism for overcoming the effects of the drug's presence (Littleton and Harper, 1990). This is thought to be a mechanism for associative conditioning, which occurs following long interdrug intervals (Cox and Tiffany, 1997). As discussed, associative conditioning has a longer time-course, and "has the potential, when exposed by the removal of the drug, to produce a functional disturbance in the opposite direction to that caused originally by the drug" (Littleton and Harper, 1990). Mechanisms subserving this process may implicate 5-HT (Ciccocioppo, 1999; Daw et al., 2002), glutamate, or neurotrophic factors (Nestler and Aghajanian, 1997), and receptor down-regulation (Nestler, 2001).

These long lasting, stable changes may even occur as a result of changes at the levels of gene expression, altering intracellular messenger pathways, which in turn alter proteins regulating transcription (Nestler, 2001). Some putative mechanisms for oppositional adaptation include up-regulation of adenosine 3',5'-monophosphate (cAMP), changes in receptor-G protein coupling, or alterations in ion channel function (Koob and Nestler, 1997; Nestler and Aghajanian, 1997). While drugs inhibit the activity of cAMP, with continued exposure the pathway recovers; upon removal of the drug, activity overshoots control levels, perhaps related to withdrawal (Nestler, 2001). These mechanisms bear a strong similarity to the notion of counteradaptation. On a molecular level, this upregulation occurs due to induction of the enzymes adenylyl cyclase and cAMP-dependent protein kinase (PKA; Nestler, 2001). In the NAcc, cAMP up-regulation has been used to account for the tolerance and dependence via the opioid peptide dynorphin (Nester, 2001), while cAMP up-regulation in the VTA appears to lead to increased GABA release, perhaps determining efficacy of counteradaptation (Self, 1997). cAMP regulation also occurs in other regions implicated in addiction (e.g., the amygdala; Nestler, 2001) Also, different receptor subtypes have different effects: D1 receptors stimulate cAMP while D2 receptors inhibit it, via association with inhibitory G proteins (Self, 1997). At the transcriptional level, these adaptations may be mediated by the drug-regulated transcription factor cAMP response element binding protein (CREB). CREB is relatively short-acting, lasting for up to a week following drug use termination, suggesting it may be implicated in the process of withdrawal (Nestler, 2001).

Current research suggests that the ΔFosB transcription factor may be responsible for mediating the effects of long-term drug sensitization (Nestler, 2001). Acute drug administration causes rapid induction of the ΔFosB transcription factor (in a range of 1-4 hours), which, due to its high stability, accumulates with repeated administration. ΔFosB is relatively longer lasting in the brain; in fact it is the "longest-lived molecular adaptation known to occur in response to a drug of abuse" (Nestler, 2001), making it a good candidate for mediation of relatively long-lasting changes in the brain following drug abuse (Berridge and Robinson, 1995). ΔFosB acts via the AMPA glutamate receptor subunit. Nestler (2001) notes that ΔFosB expression has been associated with increases in drug-seeking behaviour, self-administration, locomotion, and other rewarding responses to both cocaine and morphine. As Nestler (2001) notes, the CREB and ΔFosB transcription factors appear to work in opposition, as would be expected for mechanisms mediating tolerance and sensitization, respectively. While these changes in transcription factors are relatively enduring, it is likely that the lasting effects of drugs on the brain are mediated by actual structural changes in the brain (Nestler, 2001). A number of lines of evidence suggest the extended amygdala may be a primary site of drug sensitization for most drugs of abuse (Koob and Le Moal, 1997).

Given the nature of these potentially long-term changes to the mesocorticolimbic system, cognitive, affective, and behavioural alterations are also associated with craving.

Evidence Linking the Mesocorticolimbic System with the Craving Dimensions

Known predictors of addiction liability have been linked to mesocorticolimbic functioning. In fact, some authors have explained discrepancies in findings between different subgroups of individuals as reflecting altered biological correlates of temperament traits (Hansenne et al., 2002). At least one study found personality variables to be more important than either physiological or biochemical parameters in predicting craving (Reuter and Netter, 2001).

As noted above, the increased efficiency of the opposing system extends into *prediction of reward onset* (Mirenowicz and Schultz, 1994; Schultz et al., 1997, 2000). Both prediction and reward are, therefore, critical to the craving process. Deficits in these two processes also seem to be reflected in some of the psychological manifestations of drug dependence, including obsessionality, increased aggression, novelty seeking, and stress. These observations lead to the hypothesis that defects in the same neural mechanisms may lie at the heart of both cravings and impaired psychological processes in addiction. Numerous studies link affective, cognitive, and behavioural dimensions of dependence to the mesocorticolimbic system[7].

Affective Function

Kelley and Berridge (2002) note that three alterations of the brain reward systems can play a role in addiction: Exploitation of the brain's natural reward pathways; alterations in either quality or intensity of normal reward processes; or changes in the value of aversive withdrawal states.

The course of addiction has been studied extensively with regard to processes such as reinforcement and withdrawal. Some authors suggest that the study of negative reinforcement is unnecessary for an understanding of addiction, arguing that drug-taking can be explained solely via mechanisms of positive reinforcement (Wise, 1988). Hence, mechanisms such as sensation seeking, which appears to correlate with subjective pleasure (Martin-Soelch et al., 2001), play a role. Negative reinforcers, including negative affect and stress, also motivate drug use behaviour. These areas and their neurobiological underpinnings are examined below. It should be clear, however, that psychological definitions of terms such as "negative affect" encompass states of both anxiety and depression; correspondingly, "positive affect" does not clearly differentiate processes of liking and wanting (Davidson, 2003).

Sensation/Novelty Seeking. Sensation seeking and novelty seeking are generally concordant, being associated with a potentially heritable (Zuckerman, 1990) behavioural tendency to approach novel stimuli. Sensation seeking is somewhat more encompassing, as it also includes the tendency to approach intense or significant (salient) stimuli (Zuckerman, 1990). Sensation seekers are thought to excel at tasks in which exploratory behaviour and activation are adaptive, but do poorly in tasks which require inhibitory control (Zuckerman, 1990). Similarly, novelty seeking has been associated with disorderly conduct, impulsivity, and experience seeking (Berman et al., 2002).

Sensation seeking appears to be a common trait in multiple addictive behaviours: Equivalent levels of sensation seeking have been noted in alcoholics, cocaine addicts, and compulsive gamblers (Castellani and Rugle, 1995). Supporting the notion of a pre-existing susceptibility to addictive behaviour, sensation seekers experiment more with drugs (Berman et al., 2002; Cloninger, 1988), and begin to experiment at an earlier age (Zuckerman, 1979). Normal individuals with high novelty seeking scores demonstrate greater elevations in mood, and marginally significant increases in speech, in response to repeated d-amphetamine administration (Sax and Strakowski, 1998). Some authors argue that novelty seeking might represent a pre-existing vulnerability to DA-mediated drug wanting, which is aggravated by repeated drug use (Leyton et al., 2002), while others suggest that prolonged dependence results in changes such that dependent individuals require greater stimulation for activation of brain regions associated with reward (Martin-Soelch et al., 2001).

Most studies point to the conclusion that exposure to novelty, like drug exposure, increases DA release in the NAcc. That the novelty response is tied to DA function is suggested by studies demonstrating blocked novelty seeking behaviors following the administration of DA antagonists, (Bardo et al., 1989), as well as those showing DA efflux in the NAcc shell (with persistent DA changes in the shore) following exposure to a novel environment (Rebec et al., 1997). Also, a link between novelty seeking and DA activity was noted via apomorphine-induced release of growth hormone via D2 receptor activation in the hypothalamus (Hansenne et al., 2002). In humans, Leyton et al. (2002) found d-amphetamine-induced DA release in the ventral striatum correlated with novelty seeking. In addition, novelty seeking was also associated with self-reported "drug wanting". Animals with enhanced responses to novelty exhibit enhanced locomotor responses to amphetamine self-administration (Piazza et al., 1989), as well as to intraperitoneal injections of cocaine, and to NAcc infusions of DA (Hooks et al., 1994). These rats show increased density of D1 binding, with decreased D2 binding density, along with decreases in D2 mRNA in the NAcc, suggesting D2 down-regulation secondary to increased DA transmission (Hooks et al., 1994). These changes appeared to be specific to the NAcc.

However, other regions of the mesocorticolimbic system have also been implicated in the response to novelty. Hollerman and Schultz (1998) found that the same VTA DA neurons responsive to conditioned food reward also showed activations to novel images during learning. Alternately, it has also been suggested that alterations in novelty seeking may reflect dysfunction at the level of the PFC, as the medial and superior frontal gyri, in conjunction with the anterior cingulate and frontal eye fields, are important for directing attention to novel stimuli (Fuster, 2001). Some authors have suggested that frontal lobe damage prevents "the generation of a signal which indicates that a novel event in the environment requires additional attention" (Daffner et al., 2000). These authors found that damage in this region correlated with decreased viewing times for novel stimuli, and with apathy scores. Recent fMRI studies of novelty have also implicated the middle superior temporal gyrus (STG; Opitz et al., 1999). The authors argue that the STG is involved with the automatic detection of novel stimuli, while the frontal cortex attempts to assign meaning to the stimuli. Despite these areas of disagreement, it is clear the mesocorticolimbic system is intimately connected with responses to novel, significant stimuli.

Recent studies examining the association between genetic polymorphism and novelty seeking have linked the trait with both the D4 receptor (Ebstein et al., 1996; Van Gestel et al., 2002) and the A1 allele of the DRD2 receptor gene (Berman et al., 2002; Ratsma et al., 2001). Others have reported associations between novelty seeking and the DA transporter gene, when the DRD4 7-repeat allele was absent (Van Gestel et al., 2002), suggesting the involvement of multiple DA receptors. In contrast, studies examining the gene for the DRD3 receptor, a good candidate due to its expression in the NAcc, have not been able to conclusively link polymorphism with either addiction (alcoholism) liability, nor with related behavioural traits such as sensation seeking (Gorwood et al., 2001).

Aggression and Negative Affect. Negative affect has been described as a predisposing condition for the development of substance abuse and addiction (Pandina et al., 1992). Clinically, heightened negative affect (irritability or reactivity) has often been noted in addicts (e.g., Colder and Chassin, 1997; Dao-Castellana et al., 1998; Eisenberg and Fabes, 1992; Otter and Martin, 1996; Pandina et al., 1992). Since the propensity for negative affect is most strongly related to problems associated with substance use and having a large number of motivations for use, it has been proposed that drugs may serve as self-medication, by acting as "potent inducers of positive, and reducers of negative, affect states through direct modulation of neural circuits that inherently subserve these natural functions" (Pandina et al., 1992; Wise and Bozarth, 1987).

Mood alterations in addiction seem to be most closely tied to alterations in 5-HTergic function, although DA may also play a role (Kelley and Berridge, 2002). The significance of 5-HT is supported by findings that, "alterations of tryptophan levels give consistent results independent of whether the measure is irritability, a behavioral measure of aggression, or a self-assessment measure of quarrelsome behavior" (Young and Leyton, 2002). Tryptophan depletion is associated with decreased mood and increased aggressiveness/irritability, while supplementation is associated with increased social dominance and affiliative behaviour (see Young and Leyton, 2002, for a review). Further, oral administration of fenfluramine, a 5-HT agonist that enhances release and inhibits reuptake of the neurotransmitter, has been shown to decrease self-reported depression, hostility, and anxiety among polydrug abusers with high baseline aggression scores (Fishbein et al., 1989).

Most of the research on the role of 5-HT in aggression has been done in the context of alcohol use. Reductions in tryptophan have been noted among alcohol-preferring mice (Badawy et al., 1989), suggest that this reduction could be involved in increased levels of aggression observed during intoxication and possibly the increased incidence of depression in alcoholism (Badawy, 1996). While it has been argued that increases in aggression may be a direct result of alcohol intoxication, rather than indirectly reflecting alterations in 5-HT (Pihl et al., 1995), Schmidt and co-workers (1997) found higher plasma 5-HT levels in alcoholics with antisocial (but not depressed or anxious) personality types. Also in support of the speculation that 5-HT directly effects aggression in alcoholism, Pihl and colleagues (1995) found that lowered tryptophan levels, when paired with alcohol ingestion, resulted in increased aggression (Pihl et al., 1995). However, the authors noted that these effects appeared to be specific to situations of high arousal or stress.

Linnoila and Virkkunen (1992) suggest that the relationship between aggression and 5-HT is actually mediated by impulsivity, as individuals committing non-impulsive violent acts have lower CSF levels of the 5-HT metabolite 5-HIAA than those committing acts characterized by impulsivity. Similarly, Fishbein and colleagues (1989) found that fenfluramine had similar effects on mood whether the groups were based on baseline aggression or impulsivity scores. The authors noted that these results are consistent with, "the previously reported substantial overlap between psychometric characteristics of aggressiveness and impulsivity" (Fishbein et al., 1989).

Stress. Stress is defined as "a process involving perception, interpretation, response and adaptation to harmful, threatening, or challenging events" (Sinha, 2001), and is generally conceived of in terms of action of the hypothalamic-pituitary-adrenal (HPA) axis. In this system, stress induces the hypothalamus to release the hormones corticotrophin releasing hormone and vasopressin, prompting the anterior pituitary to release adrenocorticotrophic hormone (ACTH), culminating in cortisol secretion by the adrenal cortex. While these hormones allow activation of the system in stressful circumstances, chronic exposure is generally thought to be detrimental to well-being (Majewska, 2002). Increased cortisol secretion has been noted in response to naturally-occurring reinforcers, as well as following moderate drug intake (van Eck et al., 1996).

Individuals with a propensity for addiction are often described as "distressed, upset, nervous, and tense even in the absence of overt external stressors" (Pandina et al., 1992). Addicts have been described as fearing the intensity of their emotions, or their capability to manage them (Twerski, 1990). Indeed, researchers have found a comorbidity between substance use and personality disorders such as antisocial personality and borderline personality disorder (Rosselli et al., 2001).

The ability to cope with hypothetical situations characterized by negative affect and craving was the single best predictor of latency to relapse among abstinent smokers (Drobes et al., 1994), and a 10-year longitudinal study examining drinking motives found that "drinking to cope" with distress was significantly correlated with greater alcohol consumption and drinking problems (Holahan et al., 2001). Moreover, high baseline levels of anxiety and depression strengthened these relationships. Sinha (2001) suggests that chronic drug use may alter the individual's ability to cope with stress, increasing susceptibility to relapse. Rankin et al. (1979) found that as reported desire and difficulty in resisting alcohol increased, so did anxiety and tremor. Both of these measures correlated with a fall in blood alcohol level, and an increased speed of consumption when alcohol was later offered. Errico and co-workers (1993) examined cortisol responses in humans in response to stressors (mental arithmetic followed by a cold pressor test) in controls and alcoholics and found that, while baseline and immediate post-stressor levels were similar, alcoholics showed significantly lower serum cortisol concentrations 20 minutes post-stressor. The authors suggested that chronic HPA axis stimulation may lead to physiological adaptation via glucocorticoid receptors, resulting in a diminished cortisol response to stress. However, in terms of perceived distress, the groups did not differ, again suggesting a process of adaptation to chronic stress. In support of this conjecture, men suffering from posttraumatic stress disorder (PTSD) also show diminished cortisol levels (Yehuda et al., 1990).

Stress and anxiety have been directly linked to the mesocorticolimbic system and drug self-administration (for a review, see Marinelli and Piazza, 2002). Glucocorticoid receptors, which bind with relatively high affinity, have been discovered in the medial PFC (Diorio et al., 1993). Further, ablation of this region resulted in increased plasma ACTH and corticosterone levels, while levels were reduced in animals with corticosteroid implants into the same region, which the authors took as evidence confirming that glucocorticoid receptors in the medial PFC perform a negative feedback function on stress-induced HPA-induced activity. In rats with ibotenic lesions of the PFC, "mild subchronic [injection stress can]… induce alterations in mesolimbic DA activity that persist" (Jaskiw et al., 1990), suggesting that PFC lesions lead to a loss of modulation of subcortical DA which only become evident upon exposure to stressful circumstances (Jaskiw et al., 1990). The circuitry subserving processing of stressful events and emotional responding also implicates the amygdala, which interacts with both the NAcc, PFC (Sinha, 2001) and VTA (Pulvirenti and Diana, 2001). Lesions of the basolateral amygdala potentiate DA release in the NAcc, while decreasing release in a stress-specific manner in the PFC (Stevenson et al., 2003). Finally, numerous studies of alteration in glucocorticoid levels suggest changes in DA release in the NAcc (Marinelli and Piazza, 2002). Behaviourally, studies in mice have confirmed that animals with impaired glucocorticoid receptor function (i.e., higher levels of corticosteroids) exhibit increased locomotor activity, and higher rates of mesolimbic DAergic activity upon morphine administration (Spanagel et al., 1996). At the same time, a number of experiments have demonstrated that suppression of corticosterone decreases psychostimulant self-administration (Marinelli and Piazza, 2002).

While it may be argued that differences in the HPA axis could either result from or lead to chronic drug abuse (Errico et al., 1993), stress appears to be an important predisposing factor in drug use (see Sinha, 2001 for a review). Previous mild stress has been shown to enhance exploratory locomotor activity, as has amphetamine administration, and the effects show cross-sensitization with one another (Antelman et al., 1980; West and Michael, 1988). This observation led Antelman and colleagues (1980) to speculate that previous exposure to amphetamine may result in abnormal behavioural responses in stressful situations and, conversely, a vulnerability to stress may predispose an individual to enhanced amphetamine responsiveness. Piazza and co-workers (unpublished observations; as described in Piazza et al., 1989) also reported higher basal corticosterone levels in rats with high responses to novelty, as compared to those with lower responses. They argued that exposure to stressful events during a critical period of development may predispose individuals to initiate drug-taking behaviour. While Majewska (2002) argued that the pattern of HPA activation found in dependent individuals could be indicative of a *hypo*active HPA system, subsequent attempts to treat cocaine addicts with dehydroepiandrosterone sulfate (DHEAS), an adrenal androgen, resulted in increased cocaine use and reduced treatment retention (unpublished observations, as described in Majewska, 2002).

Accordingly, it has been suggested that the role of stress in relapse may be by generating an internal condition similar to the state experienced during drug use (Ahmed and Koob, 1997). Similarly, Piazza and co-workers (1993) argue that there is a connection between sensation seeking behaviours and stress: "Certain individuals seek stimuli or situations that are considered stressful and consequently avoided by others" due to an increased sensitivity to the reinforcing effects of glucocorticoids. The authors found that rats would self-administer glucocorticoids at plasma levels comparable to those induced by stress; furthermore, those rats showing high levels of novelty seeking responded at a 4-fold lower dose, indicating increased sensitivity to the substance. The groups did not differ in baseline endogenous levels, indicating the novelty-seeking group was in fact more responsive to the reinforcing effects of glucocorticoids. Thus, in some individuals, stress-induced neurochemical events act as priming stimuli (Majewska, 2002). This is further supported by a study showing that adrenalectomized rats showed a significant decrease in locomotor response to novelty (Prasad et al., 1998). It is noteworthy that the role of stress appears to be specific to relapse, as it has been demonstrated that corticosterone is only responsible for cross-sensitization of repeated stress with a psychostimulant challenge when it occurs following long term abstinence, rather than in active withdrawal (Prasad et al., 1998).

Cognitive Function

It has been argued that the chief role of cognitive mechanisms in dependence is to promote continued use of the substance, "[directing] the person's thought processes… to sanction or preserve" the behaviour (Twerski, 1990). It should also be noted that some theorists have posited an important role for memory in addiction (cf. Niaura et al., 1991; White, 1996), which will not be discussed herein, but must be acknowledged as intimately related given that memory is an important component of learning. Generally, the cognitive distortions of addicts include obsession regarding the drug of choice; automaticity, or an amnestic state of consciousness during drug use; distortion in time sense; and an inability to learn from negative consequences. These shall be discussed in turn.

Obsessionality. Obsessions share phenomenological qualities with cravings, in that they have are described as intrusive, unwanted, anxiety-laden, repetitive, compelling and typically difficult to resist (Kouimtsidis, 2000). The recurrent, persistent nature of these cognitions makes them particularly problematic (Modell et al., 1992a). Interestingly, however, in obsessive-compulsive disorder (OCD), individuals appear to have insight into the inappropriateness of the obsessions, and consciously attempt to ignore, suppress, or neutralize them (Warneke, 2003), which does not necessarily appear to be true of craving. For instance, while Modell and co-workers (1992b) found significant correlations between craving for alcohol and measures of obsessionality on the (modified) Yale-Brown Obsessive Compulsive Scale, levels were significantly lower than in the OCD comparison group. The authors attributed this to the observation that the patient experiences obsessions in OCD as "senseless", whereas those for alcohol may be experienced as a legitimate, culturally-accepted "need".

In a revision of this questionnaire, termed the Obsessive Compulsive Drinking Scale (OCDS), Anton and co-workers (1995) found that alcohol consumption preceding hospitalization significantly correlated with obsessive thoughts regarding drinking. High test-retest stability of this scale suggests obsessiveness is a relatively stable trait in alcoholism. The authors argue that while "a precise definition of craving is not available, it… [seems] intuitively probable, that this obsessive-compulsive dimension is associated with the concept of craving" (Anton et al., 1995).

Obsessive-compulsive behaviour implicates the orbital frontal-subcortical circuitry (Cummings, 1995; Mega et al., 1997), particularly the caudate nucleus (Warneke, 2003). The caudate, along with the NAcc, is part of the ventral striatum, and so receives innervation from the PFC (Heimer, 2003). It is known that destruction of the orbitofrontal circuitry results in difficulty terminating behaviours (Gray, 1972; Volkow, 1997). SSRIs that appear to have anti-obsessional qualities enhance 5-HT release mainly in the orbitofrontal cortex (Blier and de Montigny, 1998). Insel (1992, as cited in Anton and Drobes, 1998) also reported enhanced activity in the dorsolateral prefrontal cortex and amygdala of OCD patients.

Like addictive behaviours, OCD symptoms are aggravated by stress, are more frequent in males, and tend to be more prevalent among left-handers (Warneke, 2003). Due to the similarities between addiction and OCD, clinicians have shown some success using similar treatment strategies, most notably extinction training, in which the individual is repeatedly presented with drug-related stimuli but prevented from drug use (Laberg and Ellertsen, 1987). This is at odds with many treatment strategies.

Automaticity. Tiffany and co-workers (see Cepeda-Benito and Tiffany, 1996; Tiffany, 1990, 1999; Tiffany and Carter, 1998; Tiffany and Drobes, 1991), on the other hand, argue that there is no reason to resort to cognitive explanations of craving in addiction. They suggest that drug use is characterized by unconscious automaticity, connecting drug abuse with “habit”. Tiffany (1990) compares the addict’s behaviour in the presence of a drug cue to an overlearned behaviour, which with practice becomes “effortless and highly coordinated”. He notes that characteristics of automatic processes, such as effortlessness, increased speed, stereotypy, stimulus-bound characteristics, involuntariness, and lack of control characterize the drug taking process (Tiffany, 1990, 1999). Furthermore, automatized actions require little cognitive effort and, once initiated, are difficult to discontinue.

To the authors, the role of cravings or "urges" is that they "represent the operation of nonautomatic cognitive processes activated to facilitate or impede the execution of automatized drug-use action schemata" (Tiffany, 1990). As such, they argue that cravings are not "direct manifestations of the motivational processes central to drug use or drug relapse" (Tiffany and Drobes, 1991), but epiphenomena surrounding use. That is, cravings occur *in parallel* to the automatic processes driving drug use behaviour (Tiffany, 1999). The author further argues that nonautomatic processes predictably occur in three situations - when individuals are learning a skill; when the automatized sequence is activated but behaviour is blocked; and when the individual is attempting to prevent execution of the automatized sequence.

Tiffany and Carter (1998) insist that their schema is tied more closely to psychobiological theories, such as incentive salience, than are observations of obsessionality, based largely on claims that "wanting can powerfully direct human behavior while the person's conscious mind remains unaware of wanting or of the motivated behavior" (Berridge and Robinson, 1995). Hence, this conceptualization suggests that cravings reflect a change of *consciousness*, rather than an actual change in the emotive processes underlying drug abuse (Berridge and Robinson, 1995). As such, this schema implicates subcortical mechanisms; complex behavioural sequences first engage the PFC, with subcortical regions subserving the behaviour over time (Fuster, 2001).

Given this posited relationship with incentive salience, areas of disagreement between the models are noteworthy. Tiffany (1990) suggests that automaticity is "characteristic of most of the daily activities of humans"; but the DA neurons underlying incentive sensitization appear to be activated solely by prediction of reward (e.g., see work of Hollerman and Schultz, 1998; Mirenowicz and Schultz, 1994; Schultz et al., 1997, 2000). Tiffany postulates that craving is "a product of higher order cognitive functions" (Tiffany, 1999), and so is limited by the individual's cognitive capacities, whereas Robinson and Berridge's studies do not. More importantly, Tiffany describes these automaticities as representing states competing with (non-automatic) urges, while Robinson and Berridge appear to think of incentive sensitization as *fundamental to* craving.

The notion of drug use as automatized behaviour does, however, suggest testable hypotheses. As Tiffany (1990) notes, a drug-user consistently faced with planning tasks (e.g., new routes for obtaining the drug, or requiring constant vigilance to avoid detection), would never achieve the expected level of automatization. Disruption of these automatized routines (e.g., asking subjects to hold a cigarette with their nonpreferred hand) would be hypothesized to lead to increased craving, declines in secondary task performance, and possible psychophysiological reactivity (Cepeda-Benito and Tiffany, 1996; Tiffany, 1990).

Distortion of Time Sense. It has been observed that addicts tend to be intolerant of delay, prone to reversals of cause and effect (Twerski, 1990), and unable to comprehend the longer-term implications of their actions (Petry et al., 1998). Petry and co-workers (1998) note that this may be because they underestimate the probability of the occurrence of delayed adverse consequences. In neuropsychological investigation, Gudeman et al. (1977), concluded that, "…the alcoholic is impaired on tasks that require ongoing integration of time-space in the immediate situation" while overlearned patterns and verbal skills remain relatively intact. To this end, Petry et al. (1998) suggested that extended time perspective may serve as a protective factor against drug initiation.

Similar cognitive impairments have been demonstrated in children with fetal alcohol effects (FAE) and fetal alcohol syndrome (FAS) (Streissguth et al., 1999). Nearly half of patients show impairment, and cognitive estimation is considered the most sensitive tool among several measures in discriminating FAS/FAE individuals from controls (Kopera-Frye et al., 1996). Moreover, Korsakoff syndrome, associated with severe alcoholism, has been shown to result in defects in cognitive estimation in general, and time estimates in particular (Brand et al., 2003). Specifically, patients generate a large number of "bizarre errors", such as estimating the duration of an average morning shower as 15s or 1hr. The authors argued that Korsakoff patients are unable to employ a "plausibility check" of their responses in the temporal domain.

This deficit in time perception has recently been investigated formally. Using the Stanford Time Perception Inventory and the Future Time Perspective task, Petry and colleagues (1998) found significantly lower scores among heroin addicts than controls on measures of future orientation and prediction. When asked to predict events in their own future, these individuals employed a greatly truncated time frame, had difficulty constructing hypothetical timelines for other individuals, and showed impairment in sequencing events.

The mesocorticolimbic system is strongly implicated in these functions. The PFC appears to be crucial to the timing of behavioural sequences; it has been argued that, "the highest-ranking function of the lateral PFC is the temporal organization of behavior" (Fuster, 2001), governing the temporal integration of behaviour by focusing attention, retrieving important contextual information, and integrating information when discontinuous. Hollerman and Schultz (1998) found that DA neurons in the VTA appear to be sensitive to temporal manipulations of reward. The authors altered the timing of reward delivery to explore the effects on DAergic neurons, and found that reward delays resulted in depression of activity at the usual time of reward and activation to reward at the new time, while early presentations were associated with neuron activation without depression at the usual time of reward. Later, Schultz and colleagues (2000) examined the role of timing in DA neurons in the ventral striatum (NAcc), and found that activations in this region would persist until the expected reward was delivered, even when it occurred earlier or later than usual. These results suggest that the DA system is responsible not only for reinforcement-related events, but also timing of these events.

Damage to the orbitofrontal regions is associated with increased deliberation times making relatively minor decisions (Krawczyk, 2002). Individuals with damage to this region are more prone to impulsive decision-making, but appear to lack insight regarding deficits in their behaviour. These results are suggestive of a deficit characterized by "excessive planning without action" (Krawczyk, 2002).

This distortion in time sense may also affect the adrenocortical system, as ongoing events have been shown to have greater effects on cortisol levels than completed events (Sinha, 2001). Hence, if the individual fails to perceive an uncomfortable or stressful event as terminated, it may result in increased levels of cortisol excretion.

Deficit in Expectancy Mechanisms. Expectancies enable an individual to produce faster, more reliable judgments based on relatively less information; in addicts, this process appears to generate maladaptive behaviour patterns. The ability to generate reasonable expectations appears to be dysfunctional in dependence. Vogel-Sprott and Fillmore (1999) suggest that while "addictive drugs activate neurological reward systems common to all individuals, differences in their expectancies may contribute importantly to susceptibility for addiction" (Vogel-Sprott and Fillmore, 1999). Flaten and Blumenthal (1999) performed a study examining expectation and the placebo effect in withdrawn caffeine users. The authors administered caffeinated and decaffeinated coffee, as well as caffeinated and regular orange juice. They demonstrated additive effects to expectancy (i.e., decaffeinated coffee) in addition to the drug effect, both in subjective measures of arousal and alertness, and physiological measures of skin conductance, supporting the contention that expectancy plays a distinct role in the addiction process. A recent PET study using a similar design examined the effects of expectancy on methylphenidate in cocaine abusers (Volkow et al., 2003). This study found significant activation in the thalamus and left anterior cingulate when individuals were expecting the drug, which was not present when they received the drug without realizing it. Importantly, a review of the placebo effect in neurological disorders noted that the DAergic projection to the NAcc appears to be vulnerable to the placebo effect (de la Fuente-Fernández et al., 2002). The authors suggest that placebo effects may be especially pronounced in disorders that have a significant DAergic component, such as addiction.

The notion of impaired expectancy mechanisms in addiction is also supported by the inability of addicts to develop "preception", defined as the capacity to take advantage of the predictability of an aversive stimulus in order to lessen its psychological impact (Iacono, 1998; Taylor et al., 1999). Preception relies on the ability to foresee and learn from negative consequences. Experiments comparing addicts and normal controls show different response patterns upon delivery of predictable aversive stimuli (e.g., Iacono, 1998), and Zuckerman (1993) reports several studies suggesting deficits in passive-avoidance learning in individuals with high sensation seeking. In a study of adolescent males, Taylor and co-workers (1999) found decreases in skin conductance reactivity with brief elevations in heart rate to predictable *vs.* unpredictable stimuli, for individuals with early alcohol, nicotine, or cannabis dependence symptoms. Iacono (1998) goes so far as to suggest that poor preception may represent a physiological marker for substance dependence vulnerability, in the absence of overt symptoms.

Note, however, that either deficits in prediction, or in perception of the stimulus as aversive, could give rise to the preception phenomenon. As such, substance use may offer tension reduction to vulnerable individuals unable to prepare for stressful stimuli (Taylor et al., 1999). Miller and Rollnick (1998) have likened this lack of awareness to a deficient "internal warning system". Clinical observations support this contention. For instance, Twerski (1990) has noted that addicts have the tendency to morbidly anticipate disaster, sabotaging their progress by leading them to use substances *in anticipation* of negative outcomes. At the same time, Lowe (1990) notes that alcoholics appear to have overly *positive* expectancies regarding the effects of drinking. Heavy drinkers are less likely to expect negative consequences to occur as a result of their drinking, and perceive them less negatively (Lowe, 1990). However, because it is tied to expectation, preception is also dependent upon the process of habituation: An individual must be able to habituate to non-threatening, unexpected stimuli in order to pay attention to more important environmental variables. This process may be abnormal in addiction.

The majority of imaging and electrophysiological evidence points to the role of the PFC in dysfunctional prediction-making, both in terms of anticipation of and preparation for events (Bechara et al., 2001; Fuster, 2001). Breiter and co-workers (1997) established a connection between expectancy, craving, and the mesocorticolimbic system. Their fMRI study indicated that the NAcc and the right insula were activated both during self-reported craving, and later at retest when individuals were *expecting* cocaine infusion. Elliott and co-workers (1997) found increased orbitofrontal activation associated with feedback in a guessing task compared to a planning task. This evidence would seem to indicate that damage to the mesocorticolimbic system is associated with expectancy deficits in drug dependence.

Behavioural Abnormalities

Craving may contribute to relapse via loss of behavioural control (Modell et al., 1992b), highlighting the link between the reward and motor systems of the brain. Derryberry and Tucker (1994) connect salience with approach-withdrawal behaviours by their contention that cortical and subcortical inputs to the limbic regions respond, "in terms of the significance or importance of incoming information… aimed at preparing an effective pattern of action". Similarly, Bindra (1969) postulated the existence of two component systems governing a "central motivational state" (Figure 2.7), in which he distinguished incentive motivation, incited by the attractiveness of an external stimulus, from drive motivation, resulting from an internal imbalance or deprivation state. His notion was that the two combine to form a central motivation state, which, in turn, generates behavioural output. As reviewed, Wise and Bozarth (1987) go so far as to claim that the ability to cause psychomotor activation is the "common denominator" of addictive substances.

While the striatum is most strongly associated with motor control, MacLean (1986) noted that the striatal complex is essential to both the evocation and performance of nonverbal communication ("displays"). Furthermore, while the NAcc is best recognized in terms of its connectivity in reward circuits, it is also linked to areas more traditionally associated with motor function, such as the substantia nigra pars compacta (SNpc). Some authors have suggested that "the coordinated activation of DA neurons would signal to their postsynaptic targets the need for processing the most salient features of a given situation… *'biasing' the selection of appropriate* *responses* to meet the demands of that situation" (White, 1996, italics added). Hence, disordered DAergic function could provide a neurophysiological basis for addictive behaviours, including behavioural sensitization, inappropriate approach, and impulsivity. These are reviewed below.

Behavioural Sensitization. Behavioural sensitization refers to the "progressive, enduring enhancement of certain stimulant-induced behaviors following repetitive drug use" (Richtand et al., 2001). In humans, some researchers have directly equated the phenomenon with craving (Kalivas et al., 1998). Animal studies point to increased behavioural activation, including locomotion and stereotypy (Antelman et al., 1980), as well as unidirectional rotation (LaHoste et al., 1988) following repeated stimulant administration. It is generally related to psychomotor stimulation, which Wise and Bozarth (1987) consider to be a common attribute of all addictive drugs (stimulant properties of depressant drugs such as opiates, barbiturates, and alcohol are seen only at low doses, or following tolerance to their sedative effects). The authors argue that this psychomotor activation is due to VTA DAergic activity.

In humans, behavioural sensitization has been empirically demonstrated following repeated d-amphetamine administration, by increased talkativeness, energy level and mood (Strakowski et al., 1996) and possibly even psychosis (Antelman et al., 1980). Interestingly, increased eye blink rate, which appears to be under DAergic modulation (Karson et al., 1983), has also been shown (Strakowski and Sax, 1998; as cited in Sax and Strakowski, 2001).

At its extreme, psychomotor stimulation is associated with stereotypy. Stereotypy is characterized by enhancement of small, repetitive movements, and is associated with DAergic activation of the nigrostriatal pathway (Wise and Bozarth, 1987). However, although behaviour characterized by stereotypy is usually repetitive, Wise (1988) notes that an animal will alter a repetitive behavioural sequence in order to obtain reward, suggesting it is not compelled to be so. Although stereotypy is more commonly studied in animal models (see Wise and Bozarth, 1987 for a review), evidence suggests that as drug use becomes compulsive, there is a tendency for the individual to narrow the repertoire of behaviours associated with it (Tiffany and Carter, 1998).

Inappropriate Approach/Withdrawal Behaviours. Gray (1972; 1987) posited the existence of a separate behavioural activation system, and a behavioural inhibition system ("BAS" and "BIS", respectively)[8]. The BAS organizes behaviour in response to stimuli that signal reward, safety cues, and novelty seeking, while the BIS dictates behaviours in response to stimuli signaling aversive events, non-reward, innate fear stimuli, and facilitates learning to withhold behaviour in order to avoid punishment (Harmon-Jones and Allen, 1997), the latter of which may be associated with preception deficits (Iacono, 1998). Similarly, Zuckerman (1990) argued that high-sensation seekers have a general tendency to approach novel stimuli, while low-sensation seekers avoid them. Lang (1995) also argued for the operation of two opponent systems governing approach and aversive behaviours. He suggested they are subserved by the NAcc and amygdala, respectively, although others have suggested a more general role for the amygdala in emotional behaviour (Mega et al., 1997; Sinha 2001). Likewise, Daw and co-workers (2002) argue that these processes may be associated with DAergic and 5-HTergic mechanisms. Abnormal activation of either system is thought to reflect increased propensity for psychopathology, given the appropriate situational cues (Harmon-Jones and Allen, 1997).

It has also been suggested that hemispheric lateralization may play a role in approach and withdrawal. Kinsbourne (1978) suggested that when the generator for some ongoing task and a given behaviour are on the same side they will collaborate more effectively, whereas on discordant tasks (i.e., with control centres in opposite hemispheres) performance will be less effective. Hence, "if the subject expects a verbal stimulus and it happens to appear on the right [rather than the left], that is advantageous because the left hemisphere's verbal processing is consistent with right turning… [whereas if he must] scan to the left, the two activities are discordant" (Kinsbourne, 1978), resulting in suboptimal performance. He further suggested the major "functional locuses [sic]" for asymmetry are orienting and consummatory behaviours. Later, Davidson (1992) argued for the existence of lateralized frontal approach and withdrawal mechanisms, with the left hemisphere governing approach behaviours, and the right governing withdrawal. Briefly, he postulated that hemispheric lateralization acts as a predisposition for the animal to behave in a certain way when confronted with a novel stimulus (Wheeler et al., 1993). In this way, competition between hemispheres was hypothesized to be reduced. It has been suggested that emotional systems (i.e., positive and negative emotions) developed afterward, mapping onto this underlying system (Schiff and Bassel, 1996).

Yet, while approach and withdrawal behaviours are central to the phenomenon of addiction, they have received generally little empirical study. Blankenship and colleagues (1998) were able to demonstrate differences in approach and avoidance learning in alcohol-preferring vs. alcohol-avoiding rats: The former group showed barpress learning deficits when appetitive training preceded aversive training, while the latter group exhibited the opposite pattern. These results suggest that alterations in approach and withdrawal may be central to addiction liability.

Disinhibited Behaviour: Compulsion and Impulsivity. Compulsive behaviours and loss of control are thought to be the hallmark of addiction (Koob and Nestler, 1997), a view largely in keeping with the notion of addiction (e.g., alcoholism) as a disease state. Since cravings have been linked with obsessional characteristics of obsessive compulsive disorder (OCD), it should come as no surprise that compulsion is also considered characteristic of addiction (Twerski, 1990). Individuals are prone to "act without thinking", in a stereotypic, stimulus bound manner, when confronted with the object of their addiction (Tiffany and Carter, 1998). Similarly, in OCD, the individual feels compelled to perform some ritualistic behaviour, which somehow reduces distress (Warneke, 2003). Accordingly, selective serotonin reuptake inhibitor (SSRI) anti-depressant drugs, including fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram, are used most often in the treatment of OCD (Blier and de Montigny, 1998).

At the same time, cravings have also been compared to and share strong co-morbidity with impulse control disorders (ICDs; Soutullo et al., 1998), such as gambling, pyromania, trichtotillomania, self-mutilation, eating disorders, and Attention-Deficit Hyperactivity disorder (ADHD). Soutullo and co-workers (1998) note that ICDs have traditionally been distinguished from OCDs by their "ego-syntonicity and a pleasurable component at the moment of expression" (Frosche and Wortis, 1954; as cited in Soutullo et al., 1998), and so bear greater subjective similarity to cravings (Soutullo et al., 1998). These authors also describe concomitant cognitive (altered states of consciousness) and emotional (associated "high" followed by guilt, depression, and fatigue) characteristics that are also relevant to addiction. The authors stress that substance use disorders probably have both impulsive and compulsive components, and suggest that it may be helpful to consider them along a compulsivity-impulsivity spectrum.

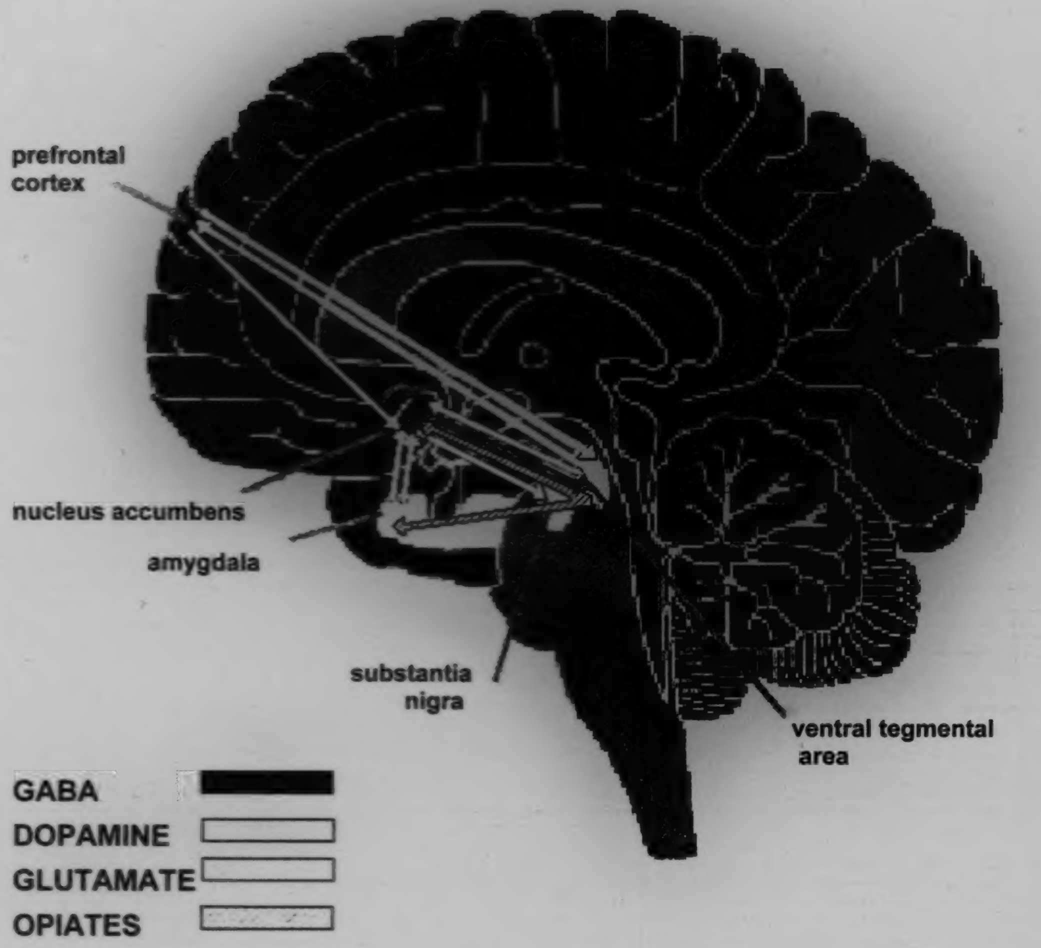
Impulsivity has alternately been referred to as behavioural disinhibition (Colder and Chassin, 1997), poor/dysregulation (Eisenberg and Fabes, 1992), or simply arousal (Pandina et al., 1992). It is routinely noted in clinical observations of individuals with a propensity for substance abuse (Butcher, 1988; Linnoila and Virkkunen, 1992; Otter and Martin, 1996), and correlates with both initiation and one-year continuation of cigarette, wine, beer, hard liquor, hashish, and depressant drugs use (Teichman et al., 1989). Further, it predicts initiation and use intensity for alcohol and marijuana (Pandina et al., 1992); accordingly, higher levels of impulse expression have been reported among hospitalized drug users (Jackson , 1996). Moreover, this relationship may be genetic. Hyperactive boys are more likely to have an alcoholic father, even when controlled for in adoption studies (Tarter and Mezzich, 1992), as are individuals who commit impulsive criminal acts (Linnoila and Virkunnen, 1992). Further, up to 20% of all hyperactive children are at risk for developing alcoholism; as such, it has been described as "the single best biobehavioural predictor of an adverse [addiction] outcome" (Wood et al., 1976, cited in Tarter and Mezzich, 1992).

On a neurochemical level, 5-HT has been implicated in various impulse control disorders, particularly suicide and compulsive behaviours, implicating the medial orbitofrontal regions (Mega et al., 1997). Depletion of 5-HT "reduces the ability of the animal to wait for the delayed reward" (Ciccocioppo, 1999). Individuals demonstrating pathological impulsive behaviour, including arson, suicide, other impulsive acts of violence, as well as type II alcoholism, have decreased CSF concentrations of the 5-HT metabolite 5-HIAA, thought to reflect 5-HT turnover in the frontal cortex (Linnoila and Virkkunen, 1992). Hence, it has been suggested that 5-HIAA may represent a marker for type II alcoholism (Linnoila et al., 1989). Moreover, fenfluramine, a 5-HT agonist, has been shown to reduce levels of anxiety, hostility, and depression in polydrug users with high baseline levels of impulsivity (Fishbein et al., 1989). For a review of the role of 5-HT in the inhibition of impulsive behaviour, the reader is directed to Ciccocioppo (1999) or Gray (1987).

Summary

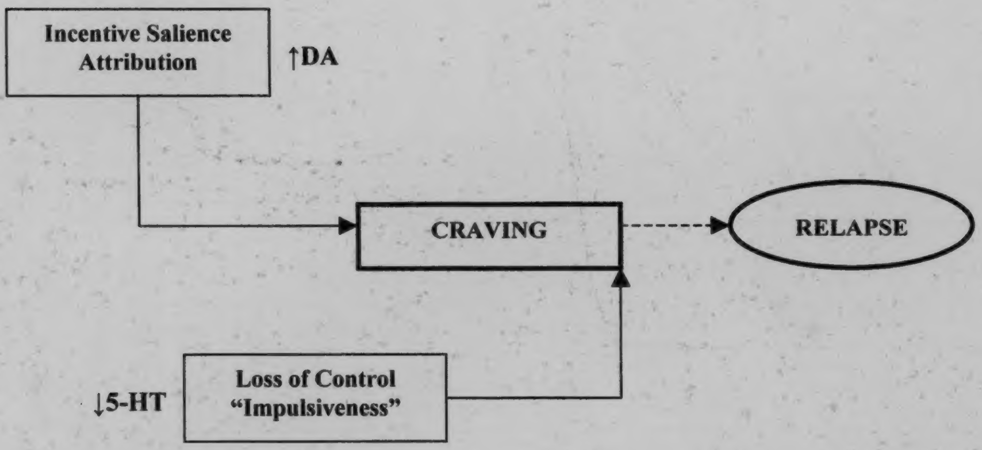
The mesocorticolimbic system is intimately involved in craving. A number of studies point to the crucial role of DA release in the NAcc, although related structures, such as the VTA, PFC, and amygdala are also implicated. Importantly, this system appears to underlie counteradaptation, a hypothesized model of how craving works in the brain. These structures are strongly related to affective, cognitive, and behavioural symptoms of addiction.

The next chapter proposes a psychobiological model of craving. The model is based on both clinical observations and neurobiological evidence, and suggests that the same neural systems that put the individual at-risk for craving may in fact predispose him to poor predictive and coping mechanisms with regard to external stressors. It does so via mechanisms of brain lateralization.


prefrontal cortex
nucleus accumbens
amygdala
substantia nigra
ventral tegmental area
GABA
DOPAMINE
GLUTAMATE
OPIATES

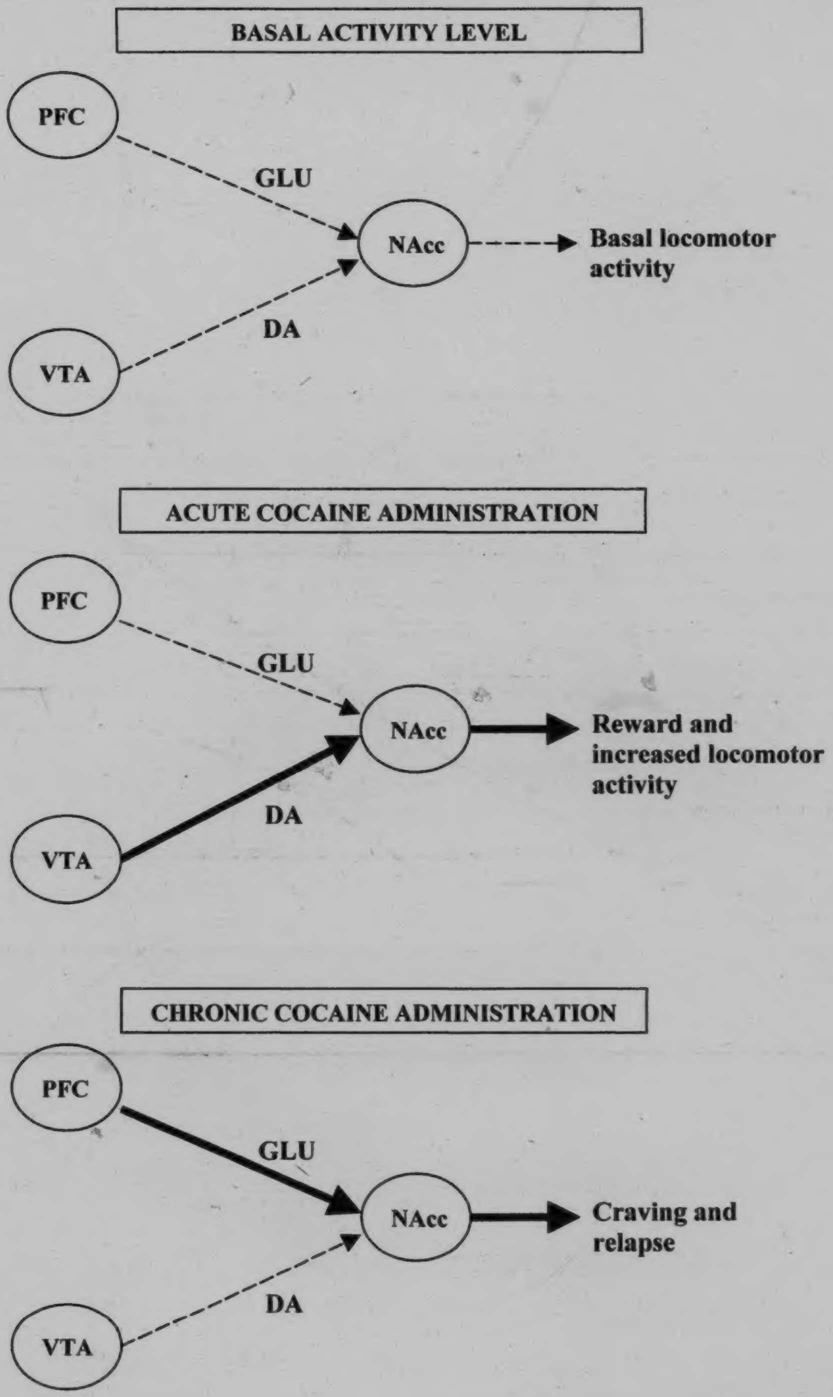
Original image source unknown

Figure 2.1 Neurochemical circuitry of the mesocorticolimbic system.


Incentive Salience Attribution
↑DA
CRAVING
RELAPSE
↓5-HT
Loss of Control "Impulsiveness"

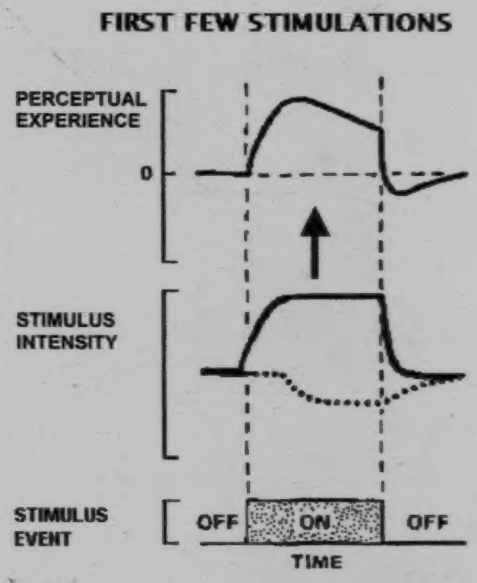
Adapted from Ciccocioppo (1999)

Figure 2.2 Putative roles of dopamine (DA) and serotonin (5-HT) transmission in relapse behaviour.


BASAL ACTIVITY LEVEL
PFC
GLU
NAcc
Basal locomotor activity
DA
VTA
ACUTE COCAINE ADMINISTRATION
PFC
GLU
NAcc
Reward and increased locomotor activity
DA
VTA
CHRONIC COCAINE ADMINISTRATION
PFC
GLU
NAcc
Craving and relapse
DA
VTA

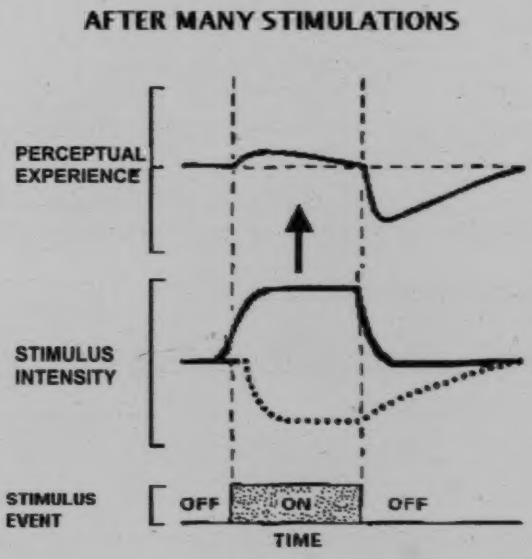
Adapted from Cornish and Kalivas (2001)

Figure 2.3 Putative roles of dopamine (DA) and glutamate (GLU) transmission in relapse behaviour.


FIRST FEW STIMULATIONS
PERCEPTUAL EXPERIENCE
0
STIMULUS INTENSITY
STIMULUS EVENT
OFF
ON
OFF
TIME

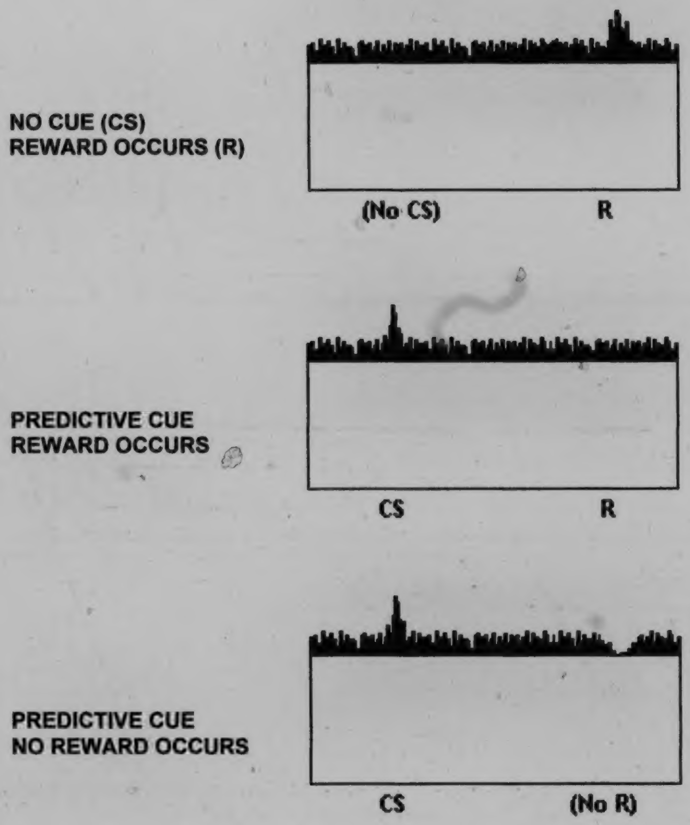
Adapted from Solomon (1991)

Figure 2.4a Solomon and Corbit's Affective Contrast Model: Novel presentation.


AFTER MANY STIMULATIONS
PERCEPTUAL EXPERIENCE
STIMULUS INTENSITY
STIMULUS EVENT
OFF
ON
OFF
TIME

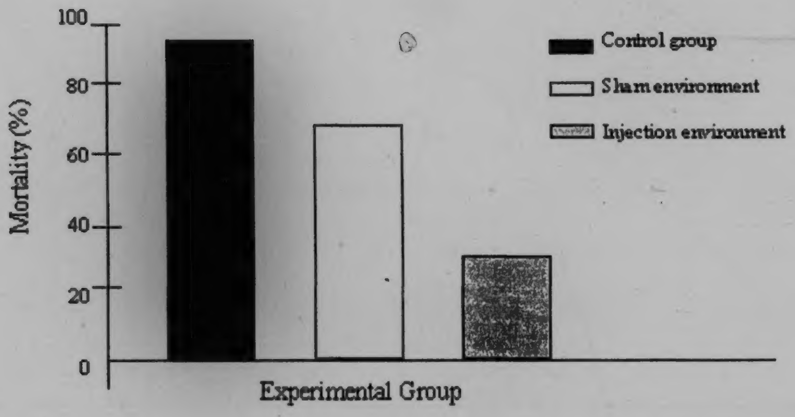
Adapted from Solomon (1991)

Figure 2.4b Solomon and Corbit's Affective Contrast Model: Habituation.



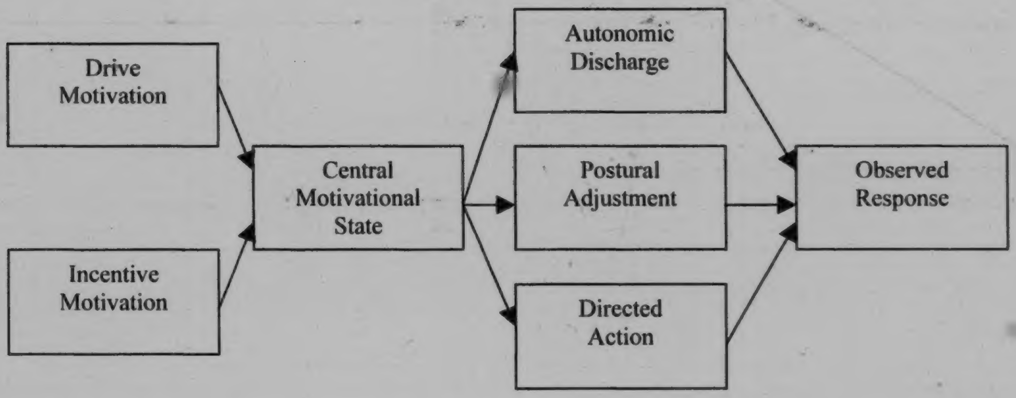
Adapted from Schultz, Dayan, and Montague (1997)

Figure 2.5 Firing of dopamine neurons to prediction of reward.



Adapted from Siegel, Hinson, Krank and McCully (1982)

Figure 2.6 Mortality rate following overdose in one of three training environments.


Drive Motivation
Incentive Motivation
Central Motivational State
Autonomic Discharge
Postural Adjustment
Directed Action
Observed Response

Adapted from Bindra (1969)

Figure 2.7 Bindra's (1969) model of Central Motivational State.

CHAPTER THREE: LATERALIZED DUAL-PATHWAY MODEL OF CRAVING

Model Rationale

The model presented in this chapter attempts to resolve some of the apparent discrepancies and contradictions found in the craving literature. Based on convergent evidence from animal, electrophysiological, and imaging studies, as well as clinical observation, it is proposed that the *two distinct types of craving* exist (see Figure 3.1). The first is more closely tied to positive reinforcement and is evident upon cue exposure while the individual is actively abusing the drug. This state peaks in early withdrawal, when continued use is uncertain, and resolves during abstinence. The second type is connected most strongly to negative reinforcement and feelings of deprivation. It is associated with recovery of function in abstinence, and appears to be activated by exposure to stressful stimuli, and as such is a causal factor in relapse.

If different *types* of cravings are hypothesized, associated with different states of use, it could resolve why some cravings appear to occur as automatized behaviours, while others are associated with distress. Tiffany and Carter (1998) conceded that, "the proposal that craving is largely unconscious… seems grossly incompatible with how addicts typically describe their desires for drugs." Indeed, the two craving types are qualitatively different in nature: Cravings associated with positive reinforcement enter consciousness as "excitement" or behavioural activation, while cravings in the deprivation state are consciously experienced as a "need". Thus, the model suggests roles for both incentive motivation and drive-reduction (Bozarth, 1990) in craving. By addressing both negative and positive reinforcement states, both of which have been empirically related to craving (Tiffany and Drobes, 1991) and figure prominently as behavioural motivators in drug abuse (Cornish & Kalivas, 2001; Sinha, 2001) but are rarely theoretically addressed, it may account for why it remains uncertain whether craving is a state of positive or negative valence (Gossop; 1990; Peers, 1996). While the active use state is associated with positive sensations and affect, during abstinence the drug becomes important for coping with negative symptoms (Laberg and Ellertsen, 1987); importantly, "craving" can occur in *either* of these states.

The model attempts to account for the general timecourse of these effects, including initial positive reinforcement, maintenance, escalation, and relapse (Pulvirenti and Diana, 2001). This is essential when attempting to describe the biological mechanisms of dependence (Nestler and Aghajanian, 1997), as the emergence of dependence in naïve individuals, and long-term relapse, are issues generally inadequately addressed in dependence theories (Wise and Bozarth, 1987). As Nader and co-workers (1997) note, "states of deprivation can switch the neurobiological substrates mediating the motivational properties of stimuli" (Nader et al., 1997). The first type of craving is observed during the initial phases of drug use, maintenance, and escalation; the second type of craving is thought to be in effect while the animal is experiencing frustrative non-reward (cf. Amsel and Roussel, 1952), with relapse triggered by acute stressors. These two time periods roughly correspond to those suggested by Cox and Tiffany (1997) as governing nonassociative and associative tolerance. The former is governed by short interdrug intervals, is not context specific, and appears to represent priming of pharmacological effects, while the latter is related to the time period in which the individual is undergoing enforced abstinence. Notably, these intervals correspond roughly with physical and psychological withdrawal. Tiffany (1990) notes that both situations are likely to result in non-automatic processing associated with craving, but with "different constellations of verbal, behavioral, and (perhaps) somatovisceral responses". Similar arguments for separable mechanisms at early *vs.* late withdrawal times have been made based on the cellular (Littleton and Harper, 1990) and animal (Prasad et al., 1998) literature. This may help to explain why some craving scales yield two separable factors predominating during withdrawal or following abstinence (Mezinskis et al., 2001). We contend that the two types of craving employ separate but related neurophysiological mechanisms, and generate their own distinctive emotional, cognitive, and behavioural sequelae, with a final common pathway of ultimate drug use.

To explain this effect, the model suggests differential roles for the left and right hemisphere in substance dependence, with activation of the left hemisphere (LH) serving as the common mechanism underlying approach behaviour (Davidson, 1992). At the same time, the model attempts to address cortical-subcortical interactions, and incorporates postulated neurochemical explanations. Because it suggests different mechanisms based on the internal state of the individual, it bears similarities to the nondeprived/deprived model (Nader et al., 1997; Nader and van der Kooy, 1997) and shares elements in common with Ciccocioppo's (1999) 2-stage model of craving. It also borrows from Bindra (1969) in positing separate roles for internal drive states *vs.* externally-motivated behaviours. In fact, the Lateralized Dual-Pathway Model of craving is not meant to be mutually exclusive of competing hypotheses; indeed, the goal is to attempt to incorporate and integrate these theoretical positions into a wider-ranging framework.

To summarize, this model posits the existence of two qualitatively different types of cravings, both of which result in drug use. This conceptualization may play a role in resolving some of the controversy surrounding craving, as one craving type may predominate in the addiction to a given drugs, or may operate via a different timecourse. A general presentation of this model precedes a more in-depth discussion of the postulated role of each hemisphere. Neuropsychological, electrophysiological, neuroimaging, and clinical evidence follow.

An Overview of Hemispheric Dysfunction in Dependence

In this model, craving is presented as a result of dysregulation of the left and right hemispheres, both of which activate the LH. We argue that it can be activated directly, via release from inhibition of a damaged right hemisphere (RH), or indirectly via activation of the hypothalamic pituitary adrenal (HPA) axis as a result of stress. The former is associated with active use, while the latter is suggested to be the basis for relapse.

We hypothesize that the prefrontal cortex (PFC) of the RH is selectively damaged in dependent individuals. Potentially, this damage is a consequence of substance use that is exacerbated in this group; alternatively, these individuals could present with a preexisting vulnerability in this region. We assume that under normal conditions the RH tonically inhibits the LH, a state that is disrupted in craving; as a result of decreased inhibition, the LH becomes overactive. That is, loss of cortical activity in the RH reduces tonic suppression contralaterally, resulting in overactivity in the left PFC. Cravings during active use have previously been described by Mezinskis and co-workers (1998) as difficulty in terminating a use episode once it has begun. Activation in the LH is associated with unconstrained approach behaviour upon cue presentation, which has been described as "the unconditioned response to all positive reinforcers" (Wise and Bozarth, 1987). The behaviour is of a stimulus-bound, compulsive nature, in line with the idea that prefrontal dysfunction results in "environmental dependency" (Cummings, 1995). This primary deficit - a shift in activation to the LH as a result of RH damage - is associated with a state of heightened arousal and sensation seeking. Craving in this state occurs upon cue presentation, and so is related to incentive-based processes.

With abstinence, there is a gradual recovery of RH activity and function, as demonstrated in neuropsychological and behavioural studies (e.g., Adams and Grant, 1986; Chelune and Parker, 1981; McCrady and Smith, 1986; Paulus et al., 2002). It is hypothesized that this recovery triggers the second category of cravings in abstinence: Generation of a deprivation state. Increased activity in the RH is experienced as a "need state", associated with negative affect, obsessionality, rumination, and anhedonia. It is also characterized by heightened anxiety. Thus, craving in this state is related to drive-reduction, presumably via increased hedonic value of the reinforcer (Kelley and Berridge, 2002; Koob and Le Moal, 1997). Because activity in the RH is associated with deprivation, it is specific to withdrawal, and so this subset of cravings is limited to experienced (rather than naïve) individuals.

This state of deprivation and anxiety grows until the individual encounters a significant stressor. If the stressor is of a considerable magnitude or duration, it activates the HPA axis (Koob and Le Moal, 1997), which has been shown to alter or even reverse cerebral asymmetries (Papousek and Schulter, 2001; for e.g. see Gruzelier et al., 1986). This results in a switch in hemispheric control, from the recovering RH to the LH. Studies of anticipatory anxiety also suggest a direct role for the LH in stress (Grillon and Davis, 1994). Hence, while it has been suggested that drug cues, exposure to the drug of abuse, and stress all play a role in drug-seeking behaviour (Self, 1997), it is assumed that the first two are critical to the active use cycle, while the third is the mechanism for relapse. Although it may seem unusual that factors such as drug cues are not more strongly related to relapse, some evidence supports this contention. For instance, Self (Roundtable discussion, 1997) notes that relapse appears to be most strongly activated by stress, followed by drug exposure, and lastly, drug cues. Again, activation of the LH is associated with a propensity for approach behaviour.

Hence, the Lateralized Dual-Pathway Model of craving postulates that activation of the LH, whether directly via RH hypoactivity, or indirectly via triggering of the HPA axis, is responsible for behavioural activation. LH activation results when either a drug-cue (e.g., Maas et al., 1998), or significant stressor (Tucker et al., 1978; Tyler and Tucker, 1982) is encountered. This hemispheric dysregulation could be conceived of a loss of normal "gain control", culminating in the inability to return to homeostasis following perturbation. The highs and lows experienced by the individual become more and more unmanageable (i.e., "spiralling distress"; Koob and Le Moal, 1997) until he is eventually driven to act (i.e., find and use the drug) in an attempt to exert external regulation. As Miller and Goldsmith (2001) explain, "the regulation for hedonic homeostasis (e.g., normal craving) becomes reset at a point which no longer signals ordinary pleasures or reward". Cognitive and affective reactions common to addiction, including irritability, obsessiveness, and impulsivity, reflect the functioning of brain mechanisms underlying such disruptions of gain control.

Before proceeding to a discussion of the coordinated functioning of this model, it is necessary to clarify the premises and assumptions on which it is based. For the time being, four relevant points will suffice: i) Dependent individuals act and are neuropsychologically comparable to patients with damage of the RH; ii) the hemispheres tonically inhibit one another; iii) controllable/escapable stress is associated with LH activation; iv) approach behaviours, such as those governing addiction, are under LH control. This asymmetric activation can account for a number of emotional and cognitive traits of the addictive process, which are not generally accounted for neurobiologically. However, before proceeding to a discussion of these factors, we will outline evidence supporting mesocorticolimbic deficits more generally.

Frontal Lobe Mechanisms in Dependence

As discussed in the preceding chapter, neuropsychological and anatomical research suggests that addiction might represent a frontal subcortical disorder. Not only have imaging studies implicated these regions (.e.g, Marchesi et al., 1997; Stapleton et al., 1995) but the symptom profile of frontal-subcortical damage (Grafman et al., 1986; Kertesz et al., 1997; Neary, 1995) bears clear similarities to clinical symptoms observed in dependence.

Right Hemisphere Injury

Gainotti (1989) argues that the tendency to attempt to explain emotional behaviour in terms of cortical-subcortical interactions neglects evidence supporting differential roles of the LH and RH in cognitive and emotional processing. Indeed, the poor performance of alcoholics on visuo-spatial *vs*. verbal tasks has led some authors to conclude that alcoholism is associated with selective RH dysfunction (Chelune and Parker, 1981; Ciesielski et al., 1985). Electrophysiological evidence suggesting LH processing superiority in alcoholics (Flor-Henry,

1986) also supports this contention, as do some neuropsychological reports of poorer functioning of the non-dominant hand (grooved pegboard test; Schaeffer and Parsons, 1986). Higher rates of substance abuse have been noted among left-handers (Coren, 1992), perhaps due to decreased levels of monoamine oxidase (MAO) activity in male sinistrals, which has been linked with increased impulsivity, sensation seeking, and suicidal ideation (for a review, see Flor-Henry, 1986). Parenthetically, the LH is known as subserving most language functions; speculateively, overactivity in this region may help account for the "good verbal façade" sometimes reported in addicts, particularly alcoholics (Chelune and Parker, 1981).

It has been posited that these deficits may reflect pre-existing hemispheric anomalies (Ciesielski et al., 1985). There is some evidence for this interpretation, as studies with rats have shown that levels of DA metabolites in the right, but not left, medial PFC predict initiation of behavioural responding for morphine (Glick et al., 1992) and escape latency from shock delivered in a shuttlebox (Carlson et al., 1993), while right-turning behaviour (DA asymmetry with relatively poorer RH functioning) is associated with increased responsivity to species-specific stressors (Sullivan and Gratton, 1998). These predispositions suggest heightened sympathetic responsivity (Everhart and Harrison, 2002), perhaps as a result of enduring stress-induced shifts in lateralization (Adamec et al., 2001). Alternately, in susceptible individuals, abnormal lateralization (i.e., decreased cortical RH activity) may result from hypersensitivity to reinforcers. Either way, these lines of evidence suggest that individual differences in cortical lateralization play a role in susceptibility to and coping with both stress and reinforcement.

In fact, addicts exhibit a number of traits associated with RH damage (Kostandov et al., 1982), particularly in terms of mood and personality. Most recently, Tranel and co-workers (2002) examined the effects of unilateral LH *vs.* RH ventromedial damage. The authors found that, in addition to behavioural and psychophysiological task performance differences, the RH damaged group showed disturbances in social and interpersonal behaviour, including the ability to maintain employment. Specifically, disturbances in decision-making, goal-directed behaviour, and emotional functioning were observed, and were characterized by a lack of insight ("acquired sociopathy") as measured by the Iowa Rating Scales of Personality Change. Again, such traits are often encountered in the addict (Twerski, 1990). The LH damaged group showed relatively preserved performance. The authors concluded that "despite the fairly high degree of anatomical homology between the right and left sectors of the ventromedial prefrontal region… the two sides may have very asymmetric roles in higher-order functions such as social conduct, decision-making, and emotional processing - specifically, the right side of the system may be critical" (Tranel et al., 2002).

RH lesions have also been shown to result in indifference reactions, with individuals "tending to deny or make light of the extent of their disabilities", as characterized by a laissez-faire, reckless attitude, with increased rates of risk-taking (Lezak, 1995). At the extreme, there is a tendency for individuals with RH damage to manifest a seeming unawareness of their disability (anosognosia) or apathetic indifference towards it (anosodiaphoria) (Gainotti, 1989). However, RH frontal lesions do not seem to result in depression, *per se;* in fact, a review of lesion studies suggests that, in depression, the right frontal zone is generally intact (Flor-Henry, 1986), although this effect appears to be specific to the anterior regions (P. Flor-Henry, personal communication, October 28, 2003). In a study of apathy in brain damage, Andersson and co-workers (1999) found depressed mood correlated only with LH lesions, while RH lesions were directly associated with apathy, as characterized only by the *negative* symptoms of depression, i.e., amotivation, avolition and reduced emotional reactivity. Again, these behavioural traits seemingly share much in common with dependence.

RH lesions also result in difficulties with processing the emotional tone of others, and resultant behaviour is often described as "insensitive", or "lacking normal affective capacity" (Lezak, 1995). Shamay-Tsoory et al. (2003) noted deficits in empathic ability in patients with RH lesions, with the most profound deficits in individuals with damage to the ventromedial prefrontal region; these deficits were characterized by difficulty in developing a "theory of mind" - loosely, the ability to adopt the mental perspective of another individual. These authors suggested that, "the right ventromedial cortex has a unique role in integrating cognition and affect to produce the empathic response" (Shamay-Tsoory et al., 2003). Lezak (1995) notes of individuals with RH damage, "their diminished capacity for self-awareness and for emotional spontaneity and sensitivity can make them unpleasant to live with and thus more likely to be rejected by family and friends" than those with LH lesions (Lezak, 1995). Thus, RH damage may account for the addict's tendency to dismiss the concerns of those around him.

The RH also appears to be important for coping with novel stimuli (Lezak, 1995), as confirmed by recent electrophysiological (Sinai and Pratt, 2003) and fMRI (Opitz et al., 1999) studies. This role potentially helps to account for learning deficits in addicts when confronted with novel information that must be integrated into a larger cognitive scheme. In support, RH damage is associated with a "loss of coherence" (Cook, 1984), and so may play a role in generating a "goal state" (Cook, 1977).

A distortion (rather than loss) of memory has also been reported (Cook, 1984) in RH damage. In story recall, individuals with right orbitofrontal damage demonstrated a tendency to both embellish certain elements and perseverate on them (Grafman et al., 1986), perhaps accounting for the tendency of addicted individuals to confabulate.

Finally, deficits in prediction and revision have been noted (Tompkins, 1991), suggesting that individuals with RH damage have difficulty in expectation development. In a study of high-risk behaviour in matched groups with LH and RH damage, the RH group was more likely to make choices based on immediate reward, even when it was accompanied by larger long-term punishment (Clark et al., 2003). Moreover, this decision-making impairment correlated with lesion volume. In contrast, individuals with LH damage were found to favour "safer" choices, and to behave more like healthy controls; further, there was no correlation in this group between behaviour and lesion size. PET studies of risky decision making in healthy controls have also pointed to activity in the right inferior and middle frontal gyri, as well as the right orbital frontal gyrus (Rogers et al., 1999). Tranel and co-workers (2002) have referred to this as a deficit in "adaptive planning for the future", which is clearly impaired in addiction.

Following a review of several neuroimaging studies, Miller and Goldsmith (2001) concluded that "the predominant correlation of craving with right but not left brain suggests laterality of reinforcing and/or conditioned responses." We suggest this activity reflects a state-dependent activation of the RH during active use. In support, Kostandov and co-workers (1982) discuss a number of electrophysiological studies (all of which involved actual alcohol ingestion) showing RH effects, with increased P300 peak latency and reduced amplitude over the right parietal cortex. This pattern of results was later confirmed by Ciesielski and co-workers (1985) using a visual processing (template-matching) task. SPECT studies confirm increases in cerebral blood flow in the right PFC during ingestion, an effect blocked by pretreatment with naloxone (Tiihonen et al., 1994). Finally, fMRI has shown increases in the ventromedial PFC on the right when pathological gamblers are given a decision-making task (Potenza et al., 2003); moreover, clear decreases in callosal activity were also evident in this group, although the authors did not comment on this effect. Interestingly, while cues are associated with increased LH activation in adolescents with alcohol use disorders, naïve controls show RH anterior activation (Tapert et al., 2003), suggesting it may be important for learning reinforcement contingencies. Overall, active use appears to be associated with activation, and concurrent disruption of, RH frontal activity.

Left Hemisphere Hyperactivity, Cravings, and Approach Behaviours

While some authors (e.g., Gainotti, 1989; Vanderploeg et al., 1987) have argued for a more general role of the RH in all emotional functioning, a number of lines of evidence suggest the LH is specialized for the positively-valenced emotions while the RH is specialized for negatively-valenced ones (Mandal et al., 1996; Pettigrew and Miller, n.d.). Clinically, Sackeim and co-workers (1982) demonstrated that individuals with LH damage (i.e., release of the RH) respond with despair, hopelessness, anger, self-blame, and pathological crying, while those with

RH damage (i.e., release of the LH) exhibit euphoric mood, symptom minimization, and social disinhibition. Furthermore, individuals displaying seizure activity, associated with regional excitation, are more likely to display uncontrollable laughter following LH seizures while pathological crying is more likely to follow RH seizures (Sackeim et al., 1982). Reports of "gourmand syndrome", a condition characterized by food cravings and preoccupations following RH damage (Regard and Landis, 1997) also support this conjecture.

Electrophysiological studies have also suggested this pattern of lateralization in affective processing. While Laurian and co-workers (1991) found generally more right-sided activation for emotionally-valenced stimuli (faces), the left frontal region showed significant activation for positive faces. Wheeler and co-workers (1993) showed that, in individuals with stable asymmetries, lateralization predicted both positive and negative emotion ratings and general affective bias, to affect-laden movie clips, even after having adjusted for baseline mood. Similarly, film clips of positive or negative valence presented to either of the two hemispheres have different effects on level of arousal, with subjects reporting more engagement when the positive film is presented to the LH or the aversive film to the RH (Wittling, 1997). These valence effects appear to be specific to the anterior regions (Heller et al., 1997).

Davidson (1992) argues that studies suggesting RH activity in all emotional functioning emphasize the *perception*, rather than experience, of emotion. He further claims that asymmetries based on affective valence predict behaviour *given an appropriate emotion elicitor*; hence, they may not be evident in studies of mood or the individual's current state. Moreover, there may be individual differences in threshold for triggering affective reactions (Wheeler et al., 1993). In Davidson's schema, frontal asymmetry is not sufficient for behavioural change - it represents a predisposition to exhibit a given emotion when confronted with an appropriate stimulus. Activation asymmetries have been shown to be relatively stable, with a test-retest correlation of .66 (Wheeler et al., 1993), supporting the notion that they represent preexisting vulnerabilities in the individual's tendency to respond in given ways. In fact, they both correctly classify asymptomatic depressive individuals in remission, and predict vulnerability in children with a positive family history (Harmon-Jones and Allen, 1997).

In addition to the differing affective roles of the hemispheres, Davidson's (1992) theory postulates that shifts in anterior activation asymmetry are associated with stable differences in *approach and withdrawal behaviour* when confronted with an appropriate stimulus. The two principles are conceptually related, as "those individuals with strong approach tendencies are also characterized as exhibiting intense positive affect in response to appropriate elicitors, whereas those subjects with strong withdrawal tendencies are likely to display intense negative affect in response to elicitors of this type" (Wheeler et al., 1993). Accordingly, scores on a measure of Gray's (1972; 1987) behavioural activation system (BAS) correlate with state positive affect, while scores reflecting the behavioural inhibition system (BIS) correlate with state negative affect (Harmon-Jones and Allen, 1997). Moreover, LH activation correlates with higher scores on the BAS (Harmon-Jones and Allen, 1997), suggesting activation asymmetries moderate appetitive and aversive behavioural tendencies. Hence, they are thought to predict the tendency of the individual to approach or withdraw from *novel or unfamiliar* conditions (Wheeler et al., 1993).

This behavioural reaction to uncertainty may be what governs the link between affect and approach/withdrawal behaviour. That is, activation of the LH may be associated with enhanced stress-resistance to uncertainty, and so it would be more likely to culminate in approach rather than withdrawal. This has some behavioural verification. In rats, path analysis confirms that increased transmission in the LH is associated with an anxiolytic effect, as demonstrated by increased time spent in both risk assessment and open arm exploration of an elevated plus maze, while increased transmission in the RH is related to reduced times (Adamec et al., 2001). Similarly, it has been shown that destruction of the left olfactory bulb, which projects to the RH via the anterior commissure, results in impairment of behavioural reaction to a stressed conspecific, suggesting that lateralization is central to the association of emotional experiences with adaptive behaviour responses (Dantzer et al., 1990). Moreover, these authors found normal pituitary-adrenal hormone levels, suggesting the behavioural effects were a direct result of altered cortical activation rather than neuroendocrine changes.

It has been proposed that a lateralized approach/withdrawal mechanism would have adaptive value ecologically, “minimiz[ing] competitive interactions” between the two response sets, with positive and negative emotions evolving out of their relationship to these behavioural responses (Schiff and Bassel, 1996). In a sense, these anterior asymmetries provide the individual with a heuristic governing behaviour, much like Damasio’s (1994) somatic marker hypothesis, also linked to frontal lobe function. However, these response tendencies are generally subtle and most often masked by behavioural compensation; bias is only revealed when the individual is preoccupied with another task (Kinsbourne, 1978), explaining why asymmetries are generally thought to reflect only “predispositions… associated with altered thresholds for behavioral reactions to [affectively-loaded] stimuli” (Tomarken et al., 1990). Thus, when LH activity is relatively higher than right, presentation of an appropriate cue culminates in approach.

We argue that once the LH is hyperactivated, behaviour takes on a compulsive nature, characterized by decreased cognition (automaticity), at which point the individual becomes “stimulus bound” and experiences loss of control. Suggestively, individuals with ventromedial PFC damage restricted mostly to the LH tend to show the most normal performance on tasks of risk-taking and decision making (Bechara et al., 2001; Clark et al., 2003; Tranel et al., 2002), likely due to the role of the right ventromedial PFC in “optimizing cautious and adaptive behavior in potentially threatening situations” (Sullivan and Gratton, 2002). Therefore, destruction of the RH PFC may result in reduced behavioural regulation. If, in fact, LH activation is associated with approach behaviour, it - by generating psychomotor activation - serves to fulfill Wise and Bozarth’s (1987) criterion of an independent, quantifiable set of observations that can predict the reinforcing effects of drugs.

In a direct test of whether hemispheric asymmetries correlated with approach or withdrawal *behaviour*, Sobotka and co-workers (1992) found that LH activation correlated with speed of approach behaviour (i.e., pressing a key^9) when attempting to win money, while RH activation correlated with withdrawal behaviour (depressing the key) when trying not to lose money. Furthermore, resting asymmetry during the interval between the warning and the cue stimulus predicted self-reported intensity of positive (although not negative) affect. In an extension of Sobotka et al.'s (1992) findings, Schiff and Bassel (1996) had individuals perform a similar task following unilateral facial muscle contractions, which the authors reported result in either self-reported sadness (left-sided contractions) or aggressive well-being (right-sided contractions). These contractions have been shown via PET to activate the contralateral anterior cingulate (Schiff et al., unpublished manuscript, 1996; cited in Schiff and Bassel, 1996). The authors found that, following right-sided (LH) contractions, and when individuals used their right hands, approach responses increased in speed whereas withdrawal responses decreased in speed; conversely, following left-sided (RH) contractions, and when using their left hands, withdrawal responses were facilitated while approach was unchanged. Again, these results generally support the notion of lateralized approach/withdrawal mechanisms.

As noted above, increased LH activity is associated with positive emotions (e.g. increased excitement, arousal, and positive interest), but it is also associated with anxiety. While this relationship may seem counterintuitive, the two states can be conceptually linked by activation of the BAS (Gray, 1972; 1987), as it is responsible for activating behaviour both in response to potential reward and in situations requiring "active avoidance" to escape punishment (Fowles, 1988). Viewed another way, both interest and anxiety may be considered appropriate reactions (Heller et al., 1997) in situations of unconstrained approach. Sinha (2001) notes that both distress and "challenge states" perceived as pleasant or exciting have been shown to activate brain stress circuitry. Similarly, Rebec and co-workers note, "some aspects of novelty can be stressful, particularly in situations *in which novelty is inescapable*" (Rebec et al., 1997, italics added). The skin conductance orienting response to novel stimuli has been linked with both of these affective dimensions (Zuckerman, 1990), which is important considering the fact that "decreased SCRs serve as a marker of susceptibility to affective disorder" (Iacono et al., 1983). More specifically, Papousek and Schulter (2001) found increased LH activity to be associated with decreased non-specific skin-conductance responses (ns-SCRs) in anxiety, while Killeen and Brady (2000) found decreased SCRs weakly correlated with self-reported craving in recently-abstinent cocaine dependent subjects. It is suggested that the common denominator among these disparate findings is activation of the LH, associated with emotional responses related to approach behaviours.

However, it should be noted that this area is still under debate (see Mandal et al., 1996 for a review). It has yet to be fully resolved whether the RH is specialized for withdrawal behaviours, for emotional communication, or simply for emotional experience. Some investigations have supported the "right hemisphere hypothesis", that the RH governs all emotional behaviour; however, it has been observed that convergent psychiatric, neurological and electrophysiological evidence make methodological or interpretive discrepancies an unlikely explanation (Pettigrew and Miller, n.d.). Hence, for this model, we assume that activity in the LH is associated with positive emotions and approach behaviour.

Cravings During Active Use: Breakdown of Contralateral Tonic Inhibition. Cook (1984) posited the importance of corticocortical homotopic inhibitory connections between the hemispheres. This is consistent with observations that "some of the corticocortical connectivity of the PFC is interhemispheric, and almost all of it is reciprocal and topologically organized" (Fuster, 2001), with the hemispheres providing "feedback control" to one another (Flor-Henry, 1992). Moreover, evidence from split-brain and callosal agenesis patients is best reconciled in terms of contralateral inhibition (Cook, 1984), as is abnormal lateralization in stress-related cardiovascular disorders (Gruzelier et al., 1986). Perhaps the strongest evidence is the patterns of emotional responsiveness following both seizure activity and brain damage, as discussed above; the fact that the same patterns of affect are noted following hemispherectomy (Sackeim et al.,

1982) effectively rules out the possibility that effects are due to changes in the ipsilateral damaged hemisphere.

This pattern of contralateral inhibition has also been demonstrated physiologically. Lateralized control of the vasomotor reflex has been demonstrated in patients with unilateral cerebral lesions (Herbaut et al., 1990). In normal controls, ischemic nerve block results in reduced cortical motor evoked potentials (MEPs) in the ipsilateral hand, but increased MEPs in the contralateral hand (Werhahn et al., 2002). Further, these homotopic contralateral (but not ipsilateral) changes are blocked by the benzodiazepine lorazepam, which enhances activity at $GABA_A$ receptors, suggesting the inhibitory transmitter is in fact implicated.

The majority of these inhibitory connections are thought to be transcallosal (Cook, 1984). Suggestively, Pfefferbaum and colleagues (1996) found significant thinning of the body and genu of the corpus callosum in older male alcoholics compared to age-matched controls[10]. This result remained even after controlling for head size, and was related to age; that is, callosal area decreased with age in alcoholics but not in normal controls. It has been suggested that callosal size is implicated in decreased amplitude of electrophysiological variables, such as the P300 (Hada et al., 2000), as seen in substance abusers. These and other authors have attributed concomitant disorganization in current source density maps of alcoholics to a disengagement of inhibitory mechanisms necessary for the efficient processing of sensory stimuli (Rodriguez Holguin et al., 1999; Hada et al., 2000).

This model predicts that LH overactivity is a direct result of a breakdown of RH tonic inhibition. Neuropsychological investigations have confirmed that, "a diminished contribution from one hemisphere may be accompanied by augmented or exaggerated activity of the other when released from the inhibitory or competitive restraints of normal hemispheric interactions [such that]… left hemisphere functioning is enhanced when the right hemisphere is impaired" (Lezak, 1995). This corresponds with Fowles (1988), who argued that the BAS and BIS are similarly under "reciprocal antagonism".

Imaging and electrophysiological studies have confirmed LH activity associated with cue-induced craving during the active use phase. Using fMRI, George and co-workers (2001) found increased activity in the left dorsolateral PFC and anterior thalamus upon cue exposure following alcohol ingestion. This increase was found only in alcoholics and not social drinkers; the group also revealed higher overall cravings for alcohol. Using a similar paradigm, Tapert and colleagues (2003) similarly reported left-sided frontal (most notably ventromedial) and limbic activation in adolescents with alcohol use disorder, upon exposure to alcohol-related cue stimuli. Another fMRI study of cue reactivity detected activation in the left dorsolateral prefrontal cortex and anterior cingulate in cocaine users (Maas et al., 1998). Further, extent (although not magnitude) of activation in these regions was found to correlate with self-reported craving. Among smokers, PET scans found increases in the left orbitofrontal cortex and midbrain, as well as the right cingulate (Martin-Soelch et al., 2001). Similarly, using an ERP paradigm, Polo and co-workers (2003) found an enhancement of the P3a waveform to novel and deviant stimuli over the left anterior cortex in alcoholics, which diminished with the number of weeks of abstinence. These authors also suggested frontal disinhibition as a mechanism. Further, among polysubstance abusers, PET studies have demonstrated correlations between the number of days since last intravenous drug self-administration and regional cerebral metabolic glucose rates in LH structures (Stapleton et al., 1995). These authors found increased activation in the left middle frontal gyrus with decreased activation on the right. At the same time, the anticraving drug naltrexone has been shown to result in rCBF decreases in the left mesial temporal region and bilateral PFC in abstinent alcoholics (Catafau et al., 1999),

That ablation of the RH is related to responses to heightened behavioural activation is supported by animal studies. In rats, ligation of the middle cerebral artery on the right has been shown to result in hyperactivity, in both spontaneous open field activity and in a running wheel, while comparable lesions on the left have no behavioural effects (Robinson, 1979). Similarly, ibotenic lesions of the RH PFC result in increased exploration of the open-arms of an elevated plus maze, and reductions in taste aversion learning (Sullivan and Gratton, 2002). Cognitively, inhibitory cortical mechanisms, thought to originate in the PFC, enable selective attention of environmental stimuli (Houghton and Tipper, 1996). This is supported by ERP studies of alcoholism (Ahveninen et al., 2000) and Attention-Deficit Hyperactivity Disorder (ADHD; Pliszka et al., 2000). Both addiction and ADHD, as well as oppositional defiant, conduct, and antisocial personality disorder, have been described as forms of disinhibited psychopathology stemming from a common deficit in inhibitory control (Iacono, 1998; Taylor et al., 1999).

Hence, this model suggests that as RH activity decreases as a result of prolonged drug use, LH increases until there is a relative shift in the overall pattern of activation. While LH lesions in humans have been associated with deficits in approach, and "loss of interest and pleasure, [with] difficulty initiating voluntary action" (Davidson, 1992), increased LH activity results in feelings of confidence, excitement, and mania (Pettigrew and Miller, n.d.), increased agitation, and impulsive behaviour. Thus, cravings during active use and early withdrawal are related to activation of the LH command centre controlling behaviour such that, even when unnecessary or inappropriate, the organism is compelled to approach the stimulus.

Cravings During Relapse: Stress-Induced LH Approach Behaviours. Studies suggest that HPA activation plays a role in relapse (Ahmed and Koob, 1997; Prasad et al., 1998; Robinson and Berridge, 1993). Specifically, "although external cues produce craving and reactivity in the laboratory, presence of negative affect, stress, and abstinence symptomatology have been [more] predictive of relapse" (Sinha, 2001). Moreover, relapse appears to be directly associated with negative affect and stress, rather than excitement or sensation seeking: Peer pressure, family/work stress, and unpleasant feelings are more than twice as likely to precipitate relapse than are positive associations (Frawley and Smith, 1992). Both depression and anxiety have been associated with hypercortisolism (Diorio et al., 1993; Sinha, 2001) perhaps resulting in increased sensitivity to the reinforcing properties of drugs (Sinha, 2001). In fact, a recent review article (Marinelli and Piazza, 2002) links glucocorticoids with relapse; adrenalectomy decreases DA concentrations in the NAcc shell, without affecting levels in the core. In fact, DA levels in the shell are selectively increased by stress, as is DA utilization in the PFC (Wightman and Robinson, 2002). As a matter of fact, Winhusen and Somoza (2001) argue that drugs affecting the HPA axis may be more effective at preventing relapse than those aimed at altering magnitude of reinforcement. It is argued that negative affect associated with deprivation, in conjunction with HPA activation, results in LH hyperactivity.

Clearly, anxiety is fairly common in abstinence; what is not so obvious is that RH activation itself is associated with "withdrawal-related psychopathology such as anxiety" (Davidson, 1992). So, as RH activity increases in recovery (Adams and Grant, 1986; Chelune and Parker, 1981; McCrady and Smith, 1986; Paulus et al., 2002), so should stress reactivity. This is in keeping with the presumed role of the RH in modulation of the sympathetic nervous system (Everhart and Harrison, 2002; Wittling, 1997). Additionally, long-term drug use changes neuroendocrine responsivity to stressors via alterations in prolactin and cortisol (Fishbein et al., 1989), leading some authors to suggest that mesocortical DA activity represents a "high level" coping mechanism in individuals with impaired negative feedback and subsequent HPA hyperfunction (Sullivan and Gratton, 1998). That is, since HPA activation is part of the organism's reaction to threatened homeostasis (Diorio et al., 1993), abstinence may trigger it because excessive drug use has altered the hedonic set point (Koob and Le Moal, 1997).

Findings of decreased cortisol levels in alcoholics in response to acute stressors suggest a physiological adaptation to chronic stress (Errico et al., 1993; see Scott and Dinan, 1998 for a similar conceptualization regarding chronic fatigue syndrome). This stress need not be conscious; *perceived* stress does not appear to be a strong predictor of cortisol levels (van Eck et al., 1996), suggesting individuals may not be aware of cumulative effects of daily stressors. Sinha (2001) links maladaptive stress responses with relapse, via decreased adaptive coping, arguing that coping is directly connected with neuroadaptation since it can be viewed as one means of regaining homeostatic control. Alcoholics are more likely than social drinkers to cite alcohol's primary benefit as being, "useful for relieving emotional distress" (Lowe, 1990). Poor generation of coping-responses in hypothetical high-risk situations seems to be the best predictor of relapse (Drobes et al., 1994), and increased levels of serum prolactin, which are elevated by psychosocial stressors, positively correlate with premature discharge from drug treatment due to non-compliance or treatment failure (Kranzler and Wallington, 1992).

Stress may also exert its effects on addictive behaviour indirectly, via alterations in cognition. Among social drinkers, anxiety was found to be the most significant predictor of neuropsychological impairment (Schaeffer and Parsons, 1986), and anxiety is more generally associated with susceptibility to distraction and reduced cognitive efficiency (Mathews et al., 1990). Drobes and colleagues (1994) hypothesize that, in situations characterized by craving and stress, the cognitive load may be too great for problem-solving required to cope with the drug stimulus. Scenarios depicting negative affect produce significantly higher ratings of self-reported stress, and lower ratings of confidence in one's ability to resist smoking (Drobes et al., 1994). They are also related to poorer effectiveness of coping responses, and a decreased likelihood of generating a coping response. At the same time, imagery-induced craving appears to result in increased heart rate and skin conductance (Cepeda-Benito and Tiffany, 1996). These studies suggest that the effort involved with maintaining abstinence is both cognitively-taxing and stressful. Alternately, Lowe (1990) suggests that drugs restrict information processing to the immediate experience, making them particularly difficult to resist in stressful situations. Either way, anxiety and associated with alterations in cognition appear to play a role in drug use.

Sinha (2001) argues that regions of the brain subserving stress and putative reward circuitry are co-activated by stressful events, suggesting they function via a common neural substrate; stress and amphetamines have been shown to be interchangeable in their ability to induce stereotypy and locomotion following repeated exposure to the other (Antelman et al., 1980). HPA axis activation appears to sensitize the drug response (West and Michael, 1988), with corticosterone playing a role in HPA modulation of DA-mediated drug effects (Piazza et al., 1993). Ciccocioppo (1999) notes, "it is possible that stress may reinstate drug self-administration (relapse), by 'priming' for the drug." At the same time, Laberg and Ellertsen (1987) found that priming doses of alcohol increase both subjective reports of craving and non-specific skin conductance responses (ns-SCRs), thought to index arousal or anxiety (Gruzelier et al., 1986); the group given the priming dose showed pronounced difficulty in rejecting a drink, an effect that was potentiated by cue exposure. SCRs also correlated with expressed "nervousness" and "uneasiness". Among abstinent cocaine users, cue exposure resulted in increased plasma cortisol levels, which correlated with both quantitative EEG measures (inversely) and self-reported anxiety (Reid et al., 2003). Skin temperature also showed a consistent reduction in the presence of cocaine-related cues, again suggestive of sympathetic activation. The finding that stress makes drug avoidance more difficult favours the notion that stressors mimic the internal state induced by the drug (Ahmed and Koob, 1997).

Asymmetric activation of the DAergic projection to the medial PFC has been noted in response to stress (Stevenson et al., 2003), suggesting that, "the nature of flow of information in these pathways differs between the two hemispheres" (Adamec et al., 2001). Indeed, Wittling (1997) demonstrated that cortisol secretion is governed by RH cortical regulation, as is sympathetic regulation of heart rate, blood pressure, and myocardial performance. Moreover, based on differences in hormonal stress responses in animals with left- *vs.* right-turning biases, LaHoste and co-workers (1988) it appears that, "individual organisms may differ in their responsivity to, and possibly in their capability to cope with, repeated stress depending on the direction of an inherent cerebral (presumably dopaminergic) asymmetry" (LaHoste et al., 1988). These differences may be preexisting. Brief daily exposure to a novel environment in infancy has been linked to a shift in paw preference favouring the RH (Tang and Verstynen, 2002). Further, early research on the effects of (stressful) infantile stimulation on rats showed that subsequent rearing in an impoverished environment resulted in heightened activity following RH ablation

(Denenberg et al., 1978). These results suggest that, in a vulnerable population characterized by RH dominance, environmental poverty - commonly cited as a contributory factor in addictive disorders - results in behavioural activation following RH injury.

However, none of this explains how stress might induce LH hyperactivity. In fact, during early abstinence, with RH recovery (and associated increases in contralateral inhibition), LH activity would be predicted to *decrease*. This was found in an rCBF SPECT scan study examining 10-day abstinent alcoholics *vs.* controls: The alcohol group had significantly lower rCBF values in the left orbitofrontal cortex, as well as the prefrontal cortex bilaterally (Catafau et al., 1999).

Tucker and co-workers (1978; Tyler and Tucker, 1983) argue that state anxiety appears to *exaggerate hemispheric lateralization biases*; if addicts rely more generally on the LH, stressor induction may result in a bias towards LH functioning, although this situation is somewhat reversed in recovery. In fact, it has been argued that the stress response is capable of switching hemispheric asymmetries in cognitive processing (Papousek and Schulter, 2001). We propose that the chief function of LH activation in response to stress is to prepare the animal for strategic action. As Marinelli and Piazza (2002) note, glucocorticoid activation during stress may reflect a compensatory response "energizing" goal-directed behaviours and increasing coping capacities. Unlike depression, stress has the potential to be a *motivational* state, since anxiety "facilitates anticipatory representations of potential dangers and alternative coping options … emphasizing the active (rather than reactive) influence of motivational states" (Derryberry and Tucker, 1994). Fowles (1988) voiced a similar conclusion, arguing that anxiety, rather than depression, is capable of activating the BAS. Suggestively, right orbitofrontal lesions are associated with "readiness to fight" with patients appearing "significantly more 'edgy' and 'reactive' to novel situations" (Grafman et al., 1986). This hypothesis may help to resolve why both LH and RH activation have been observed during state anxiety (Tankard et al., 2003): Although anxiety (and negative emotions in general) are more generally associated with RH activity, activation of the HPA axis involved with generating a *coping response* is associated with LH activation.

Animal evidence generally supports this conjecture. Sullivan and Gratton (1998) found a tendency for responsivity to some stressors (e.g., predator odour) to occur in the RH, while others (e.g., tail pinch) were specific to the left. This highlights the difference between uncontrollable stress *vs.* preventable/escapable stress. Tail pinch stress results in *behavioural adaptations* (i.e., chewing on the restraint) which, the authors argue, may result in decreases of RH activity (Stevenson et al., 2003); no such behavioural adaptation is available to the presence of predator odour in the caged animal. Using models of learned helplessness, which evaluate responses to uncontrollable stress, Carlson and co-workers (1993) confirmed increased rates of DA turnover in the PFC of the RH in animals receiving uncontrollable stress; in comparison, a group of control animals receiving identical stress which was controllable (by means of a bar press) did not show this asymmetry. Animals that escaped footshock stress exhibited a LH > RH ratio of DA, as did unshocked controls, which the authors argued might reflect a "normal" state of PFC functioning, reflective of successful coping. Conversely, increased RH activation may reflect distress when stress is unavoidable: Hughdahl and co-workers (1995) found mainly RH PFC activation in a fear conditioning paradigm characterized by inescapable stress (electric shocks received in a PET scanner). Sullivan and Gratton (1998) note that "stress-induced mesocortical DA activation proceeds from an initial left brain bias to a right brain bias as the stress is sufficiently prolonged and perceived as uncontrollable" (Sullivan and Gratton, 1998). This hypothesis suggests that stressors which are amenable to coping/escape activate the LH, which shifts back to the RH if coping attempts fail. This is in concurrence with Wittling (1997) who describes the "defense response", which is activated "when the organism is actively responding to escape from or deal with an environmental challenge… [and is] associated with activation of the left hemisphere", as opposed to the "conservation-withdrawal system" which is RH controlled, and activated when the individual passively experiences loss of control (Wittling, 1997). Likewise, Taylor and co-workers (1982) and Everhart and Harrison (2002), argue that fear (accompanied by RH sympathetic activation), is distinct from anticipatory or neurotic anxiety, the latter being associated with verbal rumination and LH activity. Note, however, that it is difficult to reconcile rumination with the effect being described here. The animal literature suggests that LH activation is associated with fixed action patterns designed to avoid/escape a stressor; clearly, rats do not require rumination for such behavioural modifications. Alternatively, verbal ruminations may represent *post hoc* attempts to account for or rationalize unanticipated impulsive behaviour. For instance, when the individual has made the "decision" to relapse, he may attempt to internally justify his decision as to "why it is okay". This links the stress-relief function of LH activation with the impulsive behaviour.

In humans, studies also link anxiety with LH activation. Studies of anxious individuals have demonstrated that high levels of state anxiety are associated with greater errors in the right visual field, while high trait anxiety is associated with a right-ear attentional bias in loudness judgments, both suggesting LH reliance (Tucker et al., 1978). The authors (Tyler and Tucker, 1982) later observed that individuals with high trait anxiety tend to show an atypical local, analytical (rather than global) processing strategy, again suggestive of LH predominance. The authors took this evidence to suggest the LH has increased susceptibility to anxiety. Electrophysiological studies support these findings. In a study of anticipatory anxiety (threat of electric shock), Grillon and Davis (1994) showed that acoustic startle effects were larger for the right ear (LH) than the left, and concomitant potentiation of the eyeblink startle response was also larger for the right eye. The authors argued that the results suggest that anxiety induced by threat of shock is mediated preferentially via the LH (Grillon and Davis, 1994).

Hence, in this model, following adequate stress, the system is overwhelmed with a preponderance of LH activity related to activation of a coping response (in the presence of already weakened RH systems), making approach behaviour particularly irresistible. We suggest that LH activation in relapse is associated with the active "seeking-out" of drug-related stimuli to relieve anxiety/negative mood state as a coping response. Note that this is subtly different than the view suggested by Davidson and co-workers (1992), who argued that LH activation is associated only with a tendency to *react* via approach behaviour given an appropriate stimulus. In the Lateralized Dual-Pathway Model, a shift in lateralization impels the individual to actively search out cues for their potential value in alleviating the stress. A similar conceptualization of the role of cues in stress-induced relapse was also put forth by Robinson and Berridge (1993).

Another distinction, in this model, is that cravings in relapse occur as a result of a transient, phasic shift in hemispheric activation, characterized by impulsivity, anxiety, and inattention. Papousek and Schulter (2001), who examined non-specific SCR levels in anxiety and depression, argue that anterior activation asymmetries "seem to be strongly affected by state factors" (Papousek and Schulter, 2001); a similar conclusion was reached by Tankard and colleagues (2003), using SPECT scanning. State anxiety also correlates with electrodermal responses to novel stimuli (Zuckerman, 1990). More directly, Volkow and colleagues (1999) found changes in metabolic activation were not common to the experimental (cocaine) group as a whole, but rather correlated with state variables such as mood and craving. This "instability" (Koob and Le Moal, 1997) is characteristic of relapse. Similar hemispheric "switching" mechanisms were proposed by Flor-Henry (1992) on the basis of fluctuations in symptomatology in OCD and bipolar disorder; specifically, he suggested that, "abnormal left hemisphere activations… 'override' as it were the striatofrontal dysregulation" (Flor-Henry, 1992) of predominantly RH activity common to these disorders. Deficient interhemispheric switching in asymptomatic bipolar disorder patients was recently confirmed using a binocular rivalry model (Pettigrew and Miller, n.d.). Recent research into cognitive processing using a technique called low-resolution electromagnetic tomography (LORETA), which locates sources of brain electrical activity, demonstrated a dynamic time course in cognitive processing with activity alternating between homologous LH and RH regions (Sinai and Pratt, 2003). This dysregulation of hemispheric activation may mark the transition from casual use to loss of control (Leshner, 1997a). It has been observed that an initial (LH-driven) behavioural lapse generates (RH) distress, resulting in a wider ranging breakdown of self-regulation (Koob and Le Moal, 1997); we argue this pattern of functioning is symptomatic of this interhemispheric switching.

Connecting such interpretations to the mesocorticolimbic system, Yang and co-workers (1996) demonstrated that the majority of PFC neurons projecting to the NAcc show intrinsic bursting, fluctuating between relative hyperpolarization and depolarization. Depolarization in the LH, characterized by increased glutamatergic drive (McFarland and Kalivas, 2001) could represent the neural counterpart for craving and loss of control in relapse (Cornish and Kalivas, 2000; 2001). Yang and co-workers (1996) note, "the membrane oscillations exhibited by… PFC neurons may synchronize the output of large groups of PFC neurons, thus allowing a coherent signal to be transmitted to subcortical areas such as the NAc[c] for response initiation" (Yang et al., 1996). This dynamic modulation may guide the choice of reinforcer (Kelley and Berridge, 2002). Recent fast-scan cyclic voltammetry recordings have supported the idea that phasic DA bursts in the NAcc, driven by excitatory amino acid inputs, are related to alerting and associative reward learning (for a review see Wightman and Robinson, 2002).

Note that this model suggests that it is not until RH activity has increased sufficiently, and only following HPA activation, that hemispheric laterality switches from the RH to the LH. Activation of this system, then, appears to be dependent upon the level of stress, perhaps reflecting the fact that glucocorticoid receptors have a low affinity for glucocorticoids, and are only activated by high corticosterone levels such as those following stress (Marinelli and Piazza, 2002). This is supported by findings that prefrontal regulation of glucocorticoid levels is stress-dependent, and appears to occur only in the presence of already heightened glucocorticoid levels (Diorio et al., 1993). In fact, it has been argued that the action of glucocorticoid hormones is "not part of the primary response to stress but… a protective compensatory response during environmental challenges" (Marinelli and Piazza, 2002). Hence, craving (associated with RH recovery) does not always result in relapse, because the individual is sometimes able to avert the stress response. It also predicts that stress-induced relapse will only occur following prolonged abstinence, as has been confirmed in adrenalectomized rats (Prasad et al., 1998).

A final consideration linking activation of drug-seeking with anxiety in relapse involves clinical anecdotal evidence regarding relapse behaviour. When the individual is in a (highly automatistic, amnestic) drug-seeking state, feelings of anxiety and panic tend to result, *if he is somehow blocked from the goal* (Tiffany, 1990). Empirically, anxiety as a response to impeded drug-use action plans has been verified by dual-task procedures of craving-related imagery, which generate increases in negative affect, arousal, and heart rate (Cepeda-Benito and Tiffany, 1996). This evidence supports the notion that craving occurs in parallel with automatic (LH) processes surrounding drug use, and is revealed, as RH deprivation symptoms, when that use is blocked (Cepeda-Benito and Tiffany, 1996). It also links craving with increases in HPA activity.

Cortical - Subcortical Interactions in Dependence

If craving-induced drug use is attributable to lateralized cortical activity, one might ask whether asymmetries extend to subcortical structures; evidence for differential patterns of lateralization in cortical and subcortical regions would help resolve apparent discrepancies between the animal and human literature (Besson and Louilot, 1995). We postulate that i) there are cortical-subcortical interactions, generally opposite in nature and ii) the subcortical effects result from asymmetries at the cortical level. An overview of the main hypothesized cortical-subcortical interactions of hemispheres in active use, withdrawal, and relapse are presented in Figures 3.2 - 3.4, respectively.

Functional asymmetries have been noted at the level of the diencephalon in a number of species and, as with humans, these asymmetries are frequently sexually-dimorphic and appear to be correlated with reinforcement-driven behaviours (Harris et al., 1996). However, the nature of the cortical-subcortical interactions is complex. Generally, drugs that enhance DAergic transmission in the PFC reduce it in the NAcc (Stevenson et al., 2003), while reduced levels of

DA transmission in the PFC are associated with augmentation of DA transmission subcortically (Sinha, 2001; Stevenson et al., 2003). For instance, 6-OHDA lesions of the basolateral amygdala potentiate DA release in response to stressor in the NAcc but attenuate release in the RH medial PFC in a stressor-specific manner (Stevenson et al., 2003). Likewise, 5-HT$_{2A}$ receptor blockers have opposing effects on haloperidol-induced DA release in the PFC and the NAcc, potentiating release in the former but abolishing it in the latter (Liégeois et al., 2002). Moreover, these changes may be hemisphere-specific: Louilot and Le Moal (1994) found changes following injections of a DA antagonist (raclopride) in the entorhinal cortex of the LH, but none following injections into the RH. Human PET studies generally support a reciprocal relationship between the limbic and cortical regions, suggesting they are "functionally linked and mutually inhibitory" (Mayberg et al., 1999).

It follows that deficits in RH cortical activity should be associated with increased ipsilateral striatal DA levels and susceptibility to drug abuse. In fact, blockade of DA activity using tetrodotoxin in the entorhinal cortex of the LH resulted in decreased DA levels in the NAcc bilaterally, while blockade in the RH was associated with a decrease in the LH NAcc, but an increase in the ipsilateral NAcc (Louilot and Le Moal, 1994). Two behavioural observations also support this hypothesis. First, rats which demonstrate leftward rotation biases develop greater behavioural sensitization in response to amphetamine, and exhibit higher levels of adrenocorticotrophic hormone (ACTH) following stress (LaHoste et al., 1988), linking asymmetric (RH) striatal DA distribution with sensitivity to psychostimulants and stress, as turning behaviours are indicative of striatal DA asymmetries (Denenberg et al, 1978; Giambalvo and Snodgrass, 1978; Wise, 1988). Similarly, in infants diagnosed with fetal alcohol syndrome (FAS) there is increased head turning to the left (Streissguth et al., 1999), an atypical rotation tendency (Kinsbourne, 1978), supporting increased DA turnover in the right NAcc in alcohol-affected infants.

Imaging studies generally support the notion of increased subcortical RH activity, and link it to craving severity. The head of the right caudate nucleus is activated when abstinent alcoholics are exposed to gustatory cues, activity which correlated significantly with self-reported desire and craving for alcohol in all 9 subjects scanned (Modell and Mountz, 1995). Similarly, a study of methylphenidate (Ritalin™), which increases DA levels, found absolute metabolic increases in the right striatum which correlated with craving while changes in the prefrontal cortex correlated with mood (Volkow et al., 1999). On the other hand, Chudasama and co-workers (2003) found evidence for *contralateral* control of the subthalamic nucleus, which receives DAergic projections from the VTA. Briefly, ablation of the medial PFC and subthalamic nucleus on opposite sides resulted in long-term cognitive deficits suggestive of attentional impairment and difficulty suppressing irrelevant responses, which was not evident when damage to the structures was ipsilateral. Thus, RH cortical damage can be expected to have both intra- and inter-hemispheric consequences.

In terms of subcortical activity, we suggest that the amygdala plays a role in stress-induced relapse. Notably, this structure sends projections to the NAcc (Cummings, 1995), VTA (Pulvirenti and Diana, 2001), and PFC (O'Doherty, 2003; Sinha, 2001), with alterations in amygdalar DA resulting in asymmetric effects in the PFC (Stevenson et al., 2003). The medial PFC modulates autonomic functions associated with stress, and also plays a negative-feedback role in regulation of the HPA axis (Sullivan and Gratton, 1998), suggested to occur via connections to the amygdala (Diorio et al., 1993). Stevenson and co-workers (2003) also suggest that HPA mediation is accomplished via the amygdala. The authors showed that destruction of the basolateral amygdala results in decreased responses to stress in the right PFC, and bilateral potentiation of responses in the NAcc, which they took to suggest that amygdalar DA exerts an inhibitory effect on stress-induced NAcc DA function; neurons containing corticotrophin-releasing factor are prominent in the extended amygdala (Heimer, 2003). In addition to its role in the stress response (Grillon and Davis, 1994), the amygdala is also involved in adaptation of goal-directed behaviour given changes in reward value (particularly the basolateral complex; O'Doherty, 2003) and attention/memory for stimuli of affective significance (Breiter et al., 1997). Porrino and colleagues (1984) found ipsilateral activation in the medial PFC and amygdala in response to ICSS in the VTA, with bilateral glucose metabolism in the mediodorsal nucleus of the thalamus which were specific to self-stimulation, and were not seen when animals were given matched experimenter-administered stimulation. These results suggest that activation is specific to learned contingencies of reinforcement. Indeed, increases in cerebral glucose metabolic rates in the right amygdala, which correlated with depression scores, were recently observed in abstinent methamphetamine abusers (London et al., 2004). These results are in keeping with the hypothesized role of the right amygdala in defensive response to threat (Adamec et al., 2001).

As mentioned, amygdalar activation tends to occur in conjunction with activation of the thalamus. The mediodorsal nucleus of the thalamus receives afferents from the amygdala, projects bidirectionally with the NAcc (Cummings, 1995), and shares reciprocal innervation with the PFC (Heimer, 2003), as part of the medial frontal-subcortical circuit. The thalamus and PFC have topologically organized connections (Fuster, 2001), with projections to layers V-VI of the PFC (Yang et al., 1996), which are, notably, most responsive to stressor-induced activation (Sullivan and Gratton, 1998). A number of craving studies report thalamic activation, typically on the right side. This seems to be more evident in younger subjects, and is associated with unilateral activation of the striatum (Martin-Soelch et al., 2001). Relative to controls, cocaine addicts show lateralized increases in the right thalamus in response to methylphenidate, which correlate with craving (Volkow et al., 1999). Similarly, Tapert and colleagues (2003) found the "strong desire" factor of their craving measure correlated with right thalamic and left temporal responses among adolescents with alcohol use disorder. An fMRI study of cue-induced alcohol craving also found increased activation in the thalamus following alcohol ingestion (George et al., 2001), as did a PET study of the effects of mCPP (Hommer et al., 1997). During acute alcohol ingestion, Tiihonen and co-workers (1994) found activation in the right PFC associated with activation in the right thalamus; activation which was not seen when individuals were pretreated with naloxone, an anti-craving drug. A recent study by Volkow and colleagues (2003) examined the effect of expectation on brain glucose metabolism, and found that thalamic responses appear specific to processes of expectation; moreover, increases significantly correlated with self-reports of high and drug liking. Responses were accompanied by unilateral decreases in activity in the cingulate, insula, and parahippocampal gyrus on the right side. These results may reflect the role of the thalamus as a relay between the NAcc and orbitofrontal cortex (Volkow et al., 2003). Taken together, these results suggest that interhemispheric transfer during relapse may be mediated by thalamic relays. Infusion of the GABA agonist muscimol into the medial thalamic nuclei has been shown to induce ipsilateral rotation (Kilpatrick et al., 1980; as cited in Taylor et al., 1982), typically associated with reduced striatal DA levels (Denenberg et al, 1978; Giambalvo and Snodgrass, 1978). Modell and Mountz (1995) go so far as to argue that increases in the right caudate nucleus may reflect the individual's attempt to inhibit drinking behaviour due to impeded inhibitory feedback to the thalamus, "hinder[ing] the subject's attempt to suppress the behavioral response to craving and result[ing] in impaired control" over consumption" (Modell and Mountz, 1995). Hence, it is posited that thalamic activation acts as the alternate pathway for LH activation, likely during abstinence. This is supported by the observation that smokers who are actively smoking *do not* show activation in the region of the thalamus (Martin-Soelch et al., 2001).

Along with increases in activity in right subcortical structures, a number of authors have reported decreases in left subcortical structures correlated with craving. Breiter et al. (1997) found decreased activation in the left amygdala correlated with self-reported craving. Also, Volkow and co-workers (1999) reported relative metabolic increases for the cingulate gyrus and cerebellum, but decreases in the left striatum, with craving. However, mCPP, a drug shown to induce cravings, results in increased glucose metabolism in the left NAcc of normal volunteers (Hommer et al., 1997). Moreover, some imaging studies provide conflicting evidence. Breiter et al. (1997) found that craving correlated with increased activation in the right parahippocampal gyrus and insula, with decreases in the left amygdala and basal forebrain, and *decreases* in the right caudate and putamen.

It might be asked why, given evidence for lateralized mechanisms in dependence, their discussion is generally neglected. Often, procedures performed (e.g., Nader and van der Kooy, 1997) or lesion sites (e.g., Bechara et al., 2001; Hooks et al., 1994) are bilateral. Sometimes, the procedures are unilateral, but not counterbalanced (e.g., Rebec et al., 1997). Furthermore, when asymmetries are encountered, there is often little attempt at explanation beyond simple description (e.g., Breiter et al., 1997; Catafau et al., 1999; Elliott et al., 1997; Hommer et al., 1997; London et al., 2004; Maas et al., 1998; Polo et al., 2003; Potenza et al., 2003; Stapleton et al., 1995; Volkow et al., 2003), even when the authors note that others have found activity in homotopic contralateral regions (e.g., George et al., 2001). This is likely because, on the surface, so many of the results appear contradictory. Additionally, lateralization studies appear to have more generally fallen out of favour.

Neurochemical Sequelae of Hemispheric Dominance: DA and 5-HT

Recently, it has been suggested that cognitive processes underlying the learning of stimulus-reward relationships may be susceptible to alterations at a neurochemical level (Rogers et al., 1999). As with the neuroanatomical evidence, there is reason to believe this modulation is asymmetric. There appear to be "bilaterally asymmetrical distributions of the major neurotransmitter systems" with reciprocal functional relationships, relating to disorders of mood and behaviour (Flor-Henry, 1986); moreover, normal asymmetries may be exacerbated by RH lesions (Regard and Landis, 1997). Robinson and Berridge (1993) remark that individual differences in hemispheric DA may alter susceptibility to incentive sensitization.

Presumably, increased rates of DA in the LH underlie behavioural activation associated with drug use. Flor-Henry reviews the evidence for a LH bias for DAergic systems, including correlations between evoked potentials over the LH and cerebrospinal fluid (CSF) concentrations of the DA metabolite homovanillic acid (HVA), as well as increased DA and GABA concentrations in the LH in humans *post mortem*, and lateral preference contralateral to the striatal cortex with higher DA concentration (respectively, Gottfries et al., 1974; and Glick et al., 1982, 1983; as cited in Flor-Henry, 1986). In a later (1992) paper, he links increased motor readiness with this DAergic LH activity. In rats, ligations of the right middle cerebral artery have been shown to result in both hyperactivity and changes in brain catecholamine levels (Robinson, 1979). Later, *in vivo* voltammetry studies confirmed a left-lateralized interdependency of the DA systems entorhinal cortex and the NAcc, associations that appeared to be both structural and chemical in nature (Louilot and Le Moal, 1994). Hence, evidence links LH activation with both behavioural activation and lateralized changes in DA systems. Likely, this activation is associated with increased salience of drug cues (cf. Robinson and Berridge, 1993).

The hypothesized neurochemical mechanism for RH recovery and depressed affect during withdrawal is reduced 5-HT transmission (Ciccocioppo, 1999). Higher levels of 5-HT metabolites, and increased imipramine binding have been reported in the medial and orbitofrontal regions of the RH post-mortem (Arato et al., 1991; as cited in Regard and Landis, 1997), and recent imaging studies have suggested an asymmetric cortical 5-HT distribution (Mann et al., 1996). This association was predicted by Flor-Henry (1986) on the basis of studies of MAO activity and rates of 5-HT turnover in sinistrals. While large increases in 5-HT are seen in the NAcc during drug binges, decreased levels in withdrawal are associated with pain, dysphoria, and depression (Koob, 1997). This interpretation is supported by findings that harm avoidance, which reflects lowered 5-HT levels (Peirson et al., 1999), is correlated with severity of depression, obsessive-compulsive disorder, and panic disorder (Berman et al., 2002). Moreover, given the role of 5-HT in satiation (Ruden, 1997), it may be fair to characterize a *lack* of 5-HT as relative deprivation. Piazza and co-workers (1993) similarly observed that 5-HT appears to limit the palatability of the reinforcer (Piazza et al., 1993), while Ciccocioppo (1999) noted that depletion of 5-HT is related to increases in the motivational value of drugs. Hence, RH hyperactivity, related to decreases in 5-HT, at once creates a "deficit state" and increases the palatability of putative reinforcers.

Another function of the 5-HT pathways appears to be inhibition of behaviour (Gray, 1987). Thus, in addition to the affective component associated with decreased 5-HT (discussed above) there is a behavioural one. Hence, in relapse, 5-HT depletion is associated with poor impulse control (Ciccocioppo, 1999). Thus, 5-HT plays a role in both the impulsive behaviour and negative mood associated with abstinence.

Taken together, these results suggest an interplay between the 5-HT and DA systems, apparently via a number of mechanisms. Suboptimal CNS 5-HT innervation results in VTA dysregulation (Bonner, 1996). At the same time, injections of a 5-HT neurotoxin (5,7-dihydroxy-tryptamine (DHT)) into the substantia nigra, which receives projections from the raphé nuclei, result in decreased ipsilateral cortical 5-HT turnover, and concomitant increases in ipsilateral striatal DA turnover (Giambalvo and Snodgrass, 1978). The authors suggested that 5-HT neurons from the raphé exert tonic inhibition at the level of the substantia nigra via direct DA synapses. More evidence for subcortical DA inhibition via 5-HT comes from studies of M100907, a selective 5-HT$_{2A}$ blocker, on DA release in the mesocorticolimbic system: While the drug potentiates DA release in the PFC induced by low doses of haloperidol, it completely blocks release in the NAcc (Liégeois et al., 2002). Notably, the drug had no effect on basal DA release, only in stimulated release under conditions where D2 receptor occupancy was relatively low. Daw and co-workers (2002) argue that there is a "natural opponency" between tonic 5-HTergic levels, which they argue govern aversive processes, and phasic DA bursts signaling reward; this conceptualization maps onto the lateralization model presented herein.

Moreover, there is an interaction between central 5-HT and the HPA axis. Some authors have suggested that 5-HT is part of the "defensive system" of the organism, triggering fight/flight responses (Daw et al., 2002). As 5-HT levels increase in the NAcc during a cocaine binge, levels of corticotrophin-releasing factor (CRF) increase in the central nucleus of the amygdala, and continue to rise following the binge (Koob, 1997). Increases in 5-HT via the agonist fenfluramine increase plasma levels of both cortisol and prolactin in aggressive, impulsive substances abusers; increases that were associated with *decreased* levels of anxiety, hostility and depression (Fishbein et al., 1989). Importantly, these subjects also had elevated baseline prolactin levels, suggesting adaptation to chronic stress (Errico et al., 1993), possibly as a result of decreases in central 5-HT (Hommer et al., 1997). Hommer and colleagues (1997) found that *m*-chlorophenylpiperazine, a mixed 5-HT agonist/antagonist, resulted in increases in subjective panic among healthy volunteers and early onset alcoholics; in the alcoholics, this was related to increases in brain glucose metabolism in the right inferior frontal gyrus and insular cortex, but, unlike the controls, no increases in the right medial and posterior orbital gyri, middle frontal gyrus, or subcortical regions. In both groups, changes in right orbital cortex glucose utilization correlated with blood levels of prolactin and ACTH. As discussed, increased serum prolactin has been linked with treatment failure and premature discharge from detoxification programs (Kranzler and Wallington, 1992). At the same time, glucocorticoids induce activity or expression of the liver enzyme tryptophan pyrrolase, leading to lower brain tryptophan concentrations (Badawy et al., 1989; Cowen, 2002).

Research with buspirone, an anxiolytic that does not appear to interact with the GABA complex, suggests that DA is also implicated in the aetiology of anxiety (Taylor et al., 1982). The authors note several studies linking diazepam, a benzodiazepine, with decreases in DA turnover in the NAcc, and decreased brain levels of HVA. They also note that injections of GABAergic ligands into the substantia nigra reticulata induce rotation, with agonistic/antagonistic properties determining whether the rotation is contralateral or ipsilateral. They suggest that the evidence supports a role for an interaction between GABA and DA, at the level of the NAcc. If DA activity is preferentially associated with LH activation (cf. Flor-Henry, 1986; 1992), these data provide evidence for the role of anxiety in provoking relapse via LH hyperactivity.

These observations support the notion of a neurochemically distinct pattern of lateralized functioning, in accordance with the Lateralized Dual-Pathway Model. However, while this model is generally internally-consistent, it is important to note that other authors (e.g., Tucker & Williamson, 1984) have suggested alternate neurochemical models somewhat at odds with the one presented herein.

Model Implications

In summary, the common denominator in craving-induced drug-related approach behaviour is LH activation. During active use, damage to the RH drives the behaviour by releasing the LH from tonic inhibition. This activation results in sensation seeking and stereotyped behaviour, compelling the animal to seek or approach the substance; hence, continued use acutely drives craving, even as it appears to satisfy it (Shiffman, 2000). In abstinence, RH activity increases, associated with craving symptoms such as depression, anxiety, and obsessionality. If sufficient stress then triggers the HPA response, it again activates the LH, generating approach behaviour.

It may be reasonable to think of the LH-related (positive reinforcement) cravings driving use in naïve, or actively-using individuals, while RH (negative reinforcement) cravings govern withdrawal and abstinence. That is, the state described as "craving" during active use is typified by LH symptoms, such as sensation seeking and stimulus-bound behaviour, upon cue presentation. Concomitant RH symptoms during active use, including denial, apathy, and lack of empathy are, by their nature, unlikely to be communicated, although they are considered classical clinical signs of addictive behaviour (Twerski, 1990). Conversely, cravings associated with abstinence are best represented by RH symptoms, such as depression and obsessionality. Associated LH symptoms, namely absentminded use, characterized by automaticity with amnestic characteristics, appear to be beneath the level of conscious awareness (cf. Tiffany, 1990, 1999), and so are not reported *per se*, although they appear to be "relevant to relapse without the person reporting it" (Goldsmith, 1998).

The existence of two craving types governed by activity in different systems helps to explain discrepancies in the research as both of these qualitatively different experiences could be described, by the addict, *as craving*. One of the two types may predominate in the dependence syndrome for a given drug. Hence, the idea that cravings are "worse" for certain classes of drugs (Halikas et al., 1991) may reflect different constellations of RH *vs.* LH symptoms. Relatedly, there may be a difference in how quickly craving shifts from one pathway to the other, depending upon the drug; again, this would result in different craving profiles at a given point of abstinence.

Because this model predicts that LH-mediated approach is most likely to occur when 5-HT levels are either at their highest (during active use) or lowest (following prolonged abstinence), is serves to explain why measures of 5-HT show associations with indices of drug use in some investigations (e.g., Hansenne et al., 2002; Van Gestel et al., 2002), but not others. (e.g., Patkar et al., 2002). Similarly, it addresses why some, but not all, studies link stress with drug use, and why states of hyper- and hypocortisolism have varying behavioural profiles, both of which appear relevant to drug dependence (Sinha, 2001). Finally, the differential roles of the hemispheres shed light on how changes in mood are related to stimulus-induced drug craving (Robinson and Berridge, 1993), and may also help to explain lower rates of substance dependence among females, who have less lateralization of function (Flor-Henry, 1986).

Furthermore, the observation that cravings are neither necessary nor sufficient for initiation of drug use is also compatible with this model. The symptom pattern associated with active use, for example, is characterized by excitement and sensation seeking, but with concomitant RH symptoms of denial, indifference, and apathy, making cravings somewhat less likely to be reported at this stage. Conversely, in abstinence, if the HPA axis is not triggered, the predicted shift in activation may not occur, and the individual will successfully avoid relapse, despite the concomitant deprivation state. Since it is relative activity of two hemispheres that drives behaviour in this model, the correlation between the cravings and behaviour reflects a common cause (hyperactivity in the LH), not because cravings cause the behaviour.

Convergent Findings

Other researchers have developed congruous explanations. Gunnarsdóttir and colleagues (2000) suggested that some individuals abuse drugs to obtain euphoric effects ("sensation seekers"), while other use them to alleviate dysphoric mood states ("self-medicators"). These are roughly comparable to the two craving types proposed herein. Using SPECT scans, the authors found that self-medicators had significantly higher levels of anxiety, with a decrease in blood flow to the left frontal cortex compared to the sensation seekers. These findings are in accordance with the model. While cravings in abstinence are thought to result in LH activation, recall this activation is periodic and state-dependent.

Berman and colleagues (2002) found that, among individuals with the A1- profile (A2/A2 genotype), novelty seeking was associated with heightened confidence, whereas among those with the A1+ allele profile (A1/A1 or A1/A2), it was associated with anticipatory worry. These results suggest that, in some individuals, activation is primarily associated with sensation seeking, while it others it is associated with self-medication: "We believe that in A1- allelic individuals, novelty seeking [NS] primarily measures the tendency to seek positive reinforcement, whereas in A1+ allelic persons NS primarily measures the tendency to seek negative reinforcement" (Berman et al., 2002). The authors also reported results of a previous study, in which the presence of the A1 allele was associated with decreases in visuospatial (RH) ability (Berman and Noble, 1997; as cited in Berman et al., 2002), supporting a LH bias in dependence characterized by anxiety.

Tiffany and Drobes' (1991) Questionnaire of Smoking Urges also suggested the existence of two factors related to craving, apparently representing positive and negative reinforcement. The former was also related to behavioural stereotypy and increased alertness, while the latter was associated with negative affect, fatigue, and discomfort surrounding abstinence. Moreover, the second factor (in withdrawal) shifted to become the 1st factor following a 6 hr abstinence with variation across deprivation state, again supporting our model.

Finally, Heyman (1996) recently proposed a theory of drug use and relapse based on the matching law. He suggested an economic process of "melioration" in drug abuse, in which local value functions take precedence over overall (net) gains, arguing that relapse reflects "the transfer of behavioral control from overall to local value functions" (Heyman, 1996). That is, while the addict understands the overall deleterious role of drugs *in principle,* relapse occurs because when drugs are available because local value functions take precedence. He suggests that drugs may induce this cognitive shift due to their immediacy and strength of feedback, intoxicating qualities, inability to satiate, strong withdrawal symptoms, and their ability to decrease the reward value of alternative reinforcers. This mechanism bears some similarity to the ventromedial PFC deficits proposed by Bechara and colleagues (1996), in which the individual persists in making disadvantageous long-term decisions based on the appeal of immediate gains. We suggest that a switch from RH to LH predominance parsimoniously accounts for such a shift on the basis of a switch from global to local processing (Lezak, 1995).

Psychological Sequelae of Hemispheric Specialization

The mesocorticolimbic circuit appears crucial for the evaluation of affective context. Frontal lobe damage is associated with environmental dependency (Cummings, 1995), and the PFC plays a role in directing activities that demand novel responses (Boller et al., 1995). Functional integrity of the PFC is thought to be crucial to behaviours governed by ambiguities and uncertainties, even after the behaviour is well learned (Fuster, 2001; Krawczyk, 2002); accordingly, Hugdahl and co-workers (1995) refer to the inferior frontal, orbito-frontal, and dorsolateral prefrontal cortex collectively as an "expectancy circuit". This coincides with neuropsychological data showing that individuals with prefrontal damage are impaired in the ability to create markers "required to associate some subsequent event with the selection of appropriate processing" (Godefroy and Rousseaux, 1997). Single-cell recordings from the orbitofrontal PFC demonstrate that lesions of the basolateral amygdala impair reinforcement-based learning, resulting in an apparent insensitivity to changes in reward value (O'Doherty, 2003). Similarly, based on studies of the orbitofrontal cortex in emotion-related learning, Shamay-Tsoory et al. (2003) predicted that impairments in these regions might results in "continued responding to a previously rewarded stimulus". This is consistent with the notion of a somatic "signal", learned from previous encounters with reward or punishment, assisting in making the best choice given the conditions of uncertainty (Bechara et al., 1996).

The striatal DA system has also been linked to decision-making governed by the PFC (Krawczyk, 2002). In the NAcc, DA levels rise "during… the *anticipatory phase of goal-driven behaviors*… [and so] are at their highest when an animal is actively seeking" a reward stimulus (Ruden, 1997), suggesting that heightened DA is directly involved in the formation of affective expectations. Young and co-workers (1993) showed that increased DA release was associated with presentation of a conditioned stimulus with a learned aversive contingency. The authors took this as an indication that the conditioned stimuli have "become salient stimuli, since they have become *predictors* of [unconditioned stimuli]… potentiated release during conditioning [being] a prerequisite for the subsequent ability of the stimulus to evoke dopamine release" (Young et al., 1993). This lead them to posit a role for the NAcc in associative conditioning. Work by Schultz and co-workers (1997, 2000; Hollerman and Schultz, 1998) supports the idea that DA neurons play a role in the prediction of reinforcement. However, while the ability of DA to focus attention towards reinforcing stimuli may aid in learning and increasing the level of arousal generally, in the overactive system, it may result in an impaired ability to focus on other potentially important aspects of the environment (Ruden, 1997). Di Chiara (1998) claims that "disadaptive responsiveness of DA transmission in the [NAcc] 'shell' elicited by drugs of abuse is therefore the common neurobiological substrate of an abnormal motivational learning process which results in excessive control over behaviour exerted by drug-related stimuli". Similarly, accumbal lesions have been shown to result in "great difficulty in reversing previously learned habits… [while] after acquisition has taken place, subsequent lesions do not impair retention" (Le Moal, 1995).

This circuitry appears to be impaired in alcohol-related disorders. Both animal and human research has shown that individuals with prenatal alcohol exposure demonstrate impaired associative learning, and deficits in inhibition, hyperactivity, increased reactivity, and perseverative behaviour (Streissguth et al., 1999). The authors found that immediately following birth FAS newborns already display poorer response modulation and decreased habituation to redundant stimuli. These findings suggest that, not only does alcohol impact this circuitry, but there is a critical period for the development of reinforcement-based learning which can be altered *in utero*; further, symptom patterns are exhibited very early and persist throughout development. These individuals appear to have particular difficulties with estimation and approximation tasks (Kopera-Frye et al., 1996), which the authors speculated are suggestive of RH lesion sites. Similar difficulties have been noted in Korsakoff patients (Brand et al., 2003), who show correlated deficits in both affective judgment and cognitive estimation.

Substance abusers tend to have positive outcome expectancies regarding use, even when they consistently experience negative consequences (Otter and Martin, 1996). Methamphetamine-dependent subjects have been shown to lack activation in the ventromedial and dorsolateral regions, the former of which correlates with performance decrements in modifying behaviour based on past outcomes (Paulus et al., 2002). These behavioural deficits, suggesting that the subjects were "supersensitive" to immediate gains at the expense of better long-range strategies, diminished with abstinence. Similarly, it has been demonstrated that "patients with prefrontal lesions do not seem to learn from previous mistakes, and they frequently engage in behaviors that lead to negative consequences, [and so] the issue of passive avoidance learning must be considered" (Bechara et al., 1996). In normal controls, a PET study of cognitive feedback in a guessing task found increased activation bilaterally in the orbitofrontal cortex as well as in the right thalamus and right insula (Elliott et al., 1997), structures implicated craving. Moreover, breakdown of this circuitry has been demonstrated in alcoholics, as an increased number of sources and sinks found in current source density analysis (Hada et al., 2000). Colder and Chassin (1997) argue that impulsive individuals are predisposed to focus on the direct reinforcing effects of the substance with little regard for possible negative consequences, a propensity which Zuckerman (1990) likens to sensation seeking, the tendency to explore novel circumstances despite attendant risks. This tendency has been described as part of a "common etiological matrix" underlying substance abuse (Butcher, 1988). In fact, Stockwell (1990) argues that the process of neuroadaptation "has no relevance to drug-related behaviours or dependence unless it is 'motivational' in some way... it has to influence an organism's expectation of the consequences of their behaviour" (Stockwell, 1990). Therefore, the process of craving is tied to the individual's expectation of reinforcement. Suggestively, Blankenship and colleagues (1998) found differences in reinforcement-based learning between alcohol-preferring and nonpreferring rats, with the former group showing learning deficits when appetitive learning took place before aversive learning. This suggests that approach-related behavioural training (previous learning context) somehow inhibited the rats' ability to learn aversive contingencies. Both current context and magnitude of predicted reinforcement appear important to the animal's perception of the reward.

However, not all learning is disrupted following asymmetric PFC lesions. For instance, lateralized ventromedial PFC lesions were found to have no effect on learning in the Morris water maze task, nor on amphetamine-induced locomotor activity, nor did they alter prepulse inhibition of the acoustic startle response (Sullivan and Gratton, 2002). However, the authors found increases in exploratory behaviour on the open arms of an elevated plus maze, and reduced taste aversion learning. The authors suggest that their results argue for a role for the right PFC in enhancing behavioural cautiousness in potentially threatening situations; i.e., they were less sensitive to aversion. Again, this interpretation fits with the model and with clinically and experimentally observed deficits noted in addicts.

We propose that lateralized mesocorticolimbic dysfunction results in a deficit characterized by problems with the development of affective expectations. Gray (1972) postulated the existence of a "comparator mechanism" checking the expected consequences of a behaviour with the actual reward/punishment obtained, resulting in either approach or withdrawal. It is proposed that lateralized frontal activity could serve as such a mechanism, with LH activation associated with approach behaviour. We propose that, in the non-addicted individual, tonic inhibition of the LH constrains approach to novel, uncertain stimuli. In the addict lacking tonic inhibition, the resultant lack of feedback control leads the individual to treat previously encountered (i.e., reward) stimuli as consistently novel. Rodriguez Holguin and co-workers (1999) reached similar conclusions based on findings of decreased P3b amplitudes in alcoholics, suggesting that chronic use results in "the inability to use available information to reduce uncertainty about the new stimulus results… [so that] each stimulus in the task is evaluated anew". The tendency to treat previously encountered stimuli as novel results in a state of hyperarousal (Gray, 1972), perhaps analogous to "apprehensive vigilance" or "anxious expectation" (Taylor et al., 1982). This heightened stress and arousal result in impairments in cognitive performance, particularly in terms of decrements in sustained attention and response inhibition. At this point behaviour begins to show signs of stereotypy and inflexibility.

We predict that dependent individuals (and likely those prone to addiction) will show differences in terms of their ability to predict and cope with unexpected affective stimuli. Similarly, Bechara and co-workers (2001) suggest that cognitive impairment in substance dependence may rely on two defective processes - one reflecting abnormal activity of the subcortical regions of the mesolimbic DA system, related to "exaggerated processing of the incentive values of substance related stimuli" (affect); the other involving the ventromedial prefrontal cortex, related to impaired inhibition of behaviour associated with immediate reward (expectation-driven behaviour). This coordinated deficit result is thought to result both in altered cognitive tendencies, (a deficit in reinforcement-based learning), and in craving. In other words, it is hypothesized that the deficit not only alters the individual's learning processes, but influences the actual drug experience. Increased behavioural drive may occur as a result of frustration if expectancy mechanisms are impaired, while increased search behaviour for additional reinforcement may result if affective mechanisms are impaired. Some possible psychological symptoms might include a lack of appreciation for the role of conditioned stimuli to trigger cravings; a change in the magnitude of the hedonic component of the drug experience and associated withdrawal symptoms; an alteration in the capacity to cope with stressors; and a failure to plan or provide for deleterious consequences in the face of current positive reinforcement.

Testing the Link Between Craving and Reinforcement-Based Learning

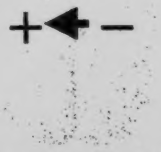
Due the their differential regulation by the left- and right-hemispheres, the processes of expectation development and affect regulation are critical to both the development of cravings and reinforcement-based learning. This common neurobiological origin carries with it an important implication: Craving and reinforcement-based learning should be correlated. This consequence gives us the opportunity to study craving indirectly, through measurement of reinforcement-based learning processes, an approach that also lessens problema of demand characteristics (Pickens and Johanson, 1992; Shiffman, 2000), semantic interpretation of responses, subjective self-deception, and retrospective recall (Shiffman, 2000). Such approaches are preferable in populations with compromised cognitive capacities or level of co-operativeness calls reliability of self-reports into question (Cunningham, 1992). Moreover, altered event related potentials (ERPs) may represent a risk marker, in the absence of overt dependence symptoms.

To study this problem, we recorded ERPs while dependent individuals performed a reinforcement-based learning task. If individuals with severe cravings show different patterns of ERPs during the task, it will establish that i) there is a measurable, physiological basis for craving and ii) there is a connection between craving and reinforcement-based learning. Our experimental design is discussed in Chapter 5. One important question is whether there is any way to ensure that the measure being used is testing the structures believed at-risk. This question is of particular importance when ERPs are employed, due to what is known as the "inverse problem"; that is, it cannot be known for certain whether the pattern of electrical activity on the scalp reflects brain activity in the directly underlying region, although imaging studies have generally supported this notion (Burgess and Gruzelier, 1997). In order to confirm the location of the neural regions involved, we used a modification of an experimental design shown to be sensitive to ventromedial prefrontal damage, as confirmed by MRI in other experiments. We also used several neuropsychological measures thought to be good indicators of frontal lobe function. In addition, we employed a number of questionnaire variables to help us study the role of mood and personality variables associated with dependence.

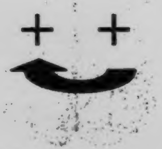
Summary

The Lateralized Dual-Pathway Model helps resolve some of the controversy surrounding the role of cravings in the etiology of drug dependence. Two phenomena, governed by different hemispheres and with a different time course, and characterized by different phenomenological experiences, have routinely been studied as one concept. Moreover, since the two types of craving occur during different stages of use behaviour (i.e., during active use *vs.* abstinence), measures of craving taken at different times may present different and conflicting clinical pictures. Symptoms associated with RH overactivity fit with models of obsessionality proposed by both Modell (1992a), and Anton's (1995) groups, while LH hyperactivity is more in line with Tiffany and Carter's (1998) conception of compulsive drug use, and the association of drug abuse with sensation seeking (Berman et al., 2002; Cloninger, 1988; Zuckerman, 1979). The model also helps explain why cravings have been associated with both dysphoria and euphoria (Peers, 1996). We suggest that this model makes specific, testable predictions regarding the nature of craving at different points in the drug use cycle.

	LH Effects	RH Symptoms
	During active use	
Affective	euphoria, excitement	apathy, lack of empathy
Cognitive	sensation-seeking, ↓concern w/ costs	denial, overconfidence indifference
Behavioural	stimulus-bound behaviours	amotivation, avolition
↺↻	**Relapse in abstinence**	
Affective	stress-relief	depression, anhedonia
Cognitive	automaticity, amnestic qualities	obsessiveness; preoccupation
Behavioural	impulsivity/ stereotypy	avoidance



Incentive-Based:
Cravings characterized by anticipation of positive reinforcement



Drive-Based:
Cravings characterized by negative reinforcement (need)

Figure 3.1 Intrahemispheric function in the Lateralized Dual-Pathway Model of Craving. Cravings associated with euphoria during active use are represented by the upper left quadrant, while related psychological symptoms of drug dependence are found in the upper right quadrant. Cravings associated with abstinence are represented by the lower right quadrant, while related behaviour during relapse is linked with the traits found in the lower left quadrant. Note, the shaded regions represent the characteristic symptoms associated with cravings of each type (positive *vs.* negative reinforcement).

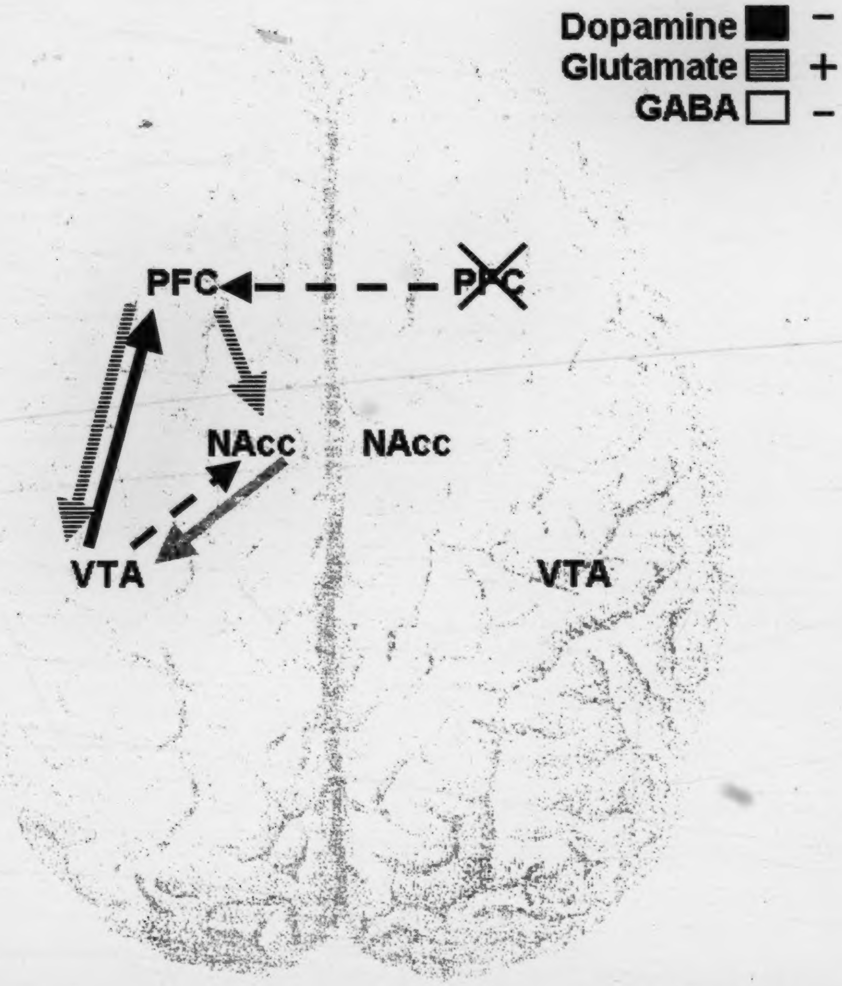

Dopamine ■ −
Glutamate ▤ +
GABA ☐ −
PFC
PFC
NAcc
NAcc
VTA
VTA

Figure 3.2 Proposed neuroanatomical transmitter changes during *active use*. Solid arrows indicate increased activity; dashed arrows indicate decreased activity (relative to baseline). Damage to the RH PFC releases the left hemisphere from tonic contralateral inhibition. This results in glutamatergic drive to the NAcc, associated with heightened responsivity to drug cues, resulting in approach behaviour.

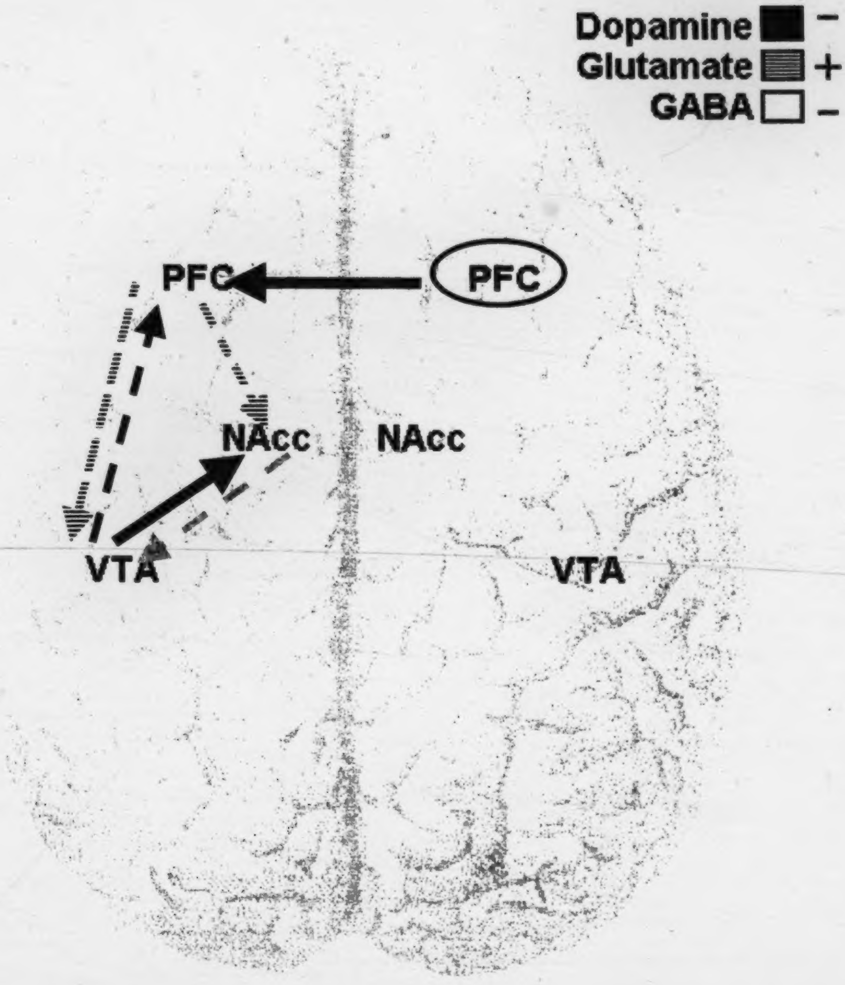

Dopamine ■ −
Glutamate ▤ +
GABA ☐ −
PFC
PFC
NAcc
NAcc
VTA
VTA

Figure 3.3 Proposed neuroanatomical transmitter changes during *withdrawal*. The circle indicates the site generating the observed effect. Recovery of the right PFC during abstinence (enhanced PFC activity) results in increased tonic inhibition of LH consistent with avoidance behaviour. As levels of LH activity drop (a relative RH increase), a preponderance of RH activity is associated with the deprivation state.

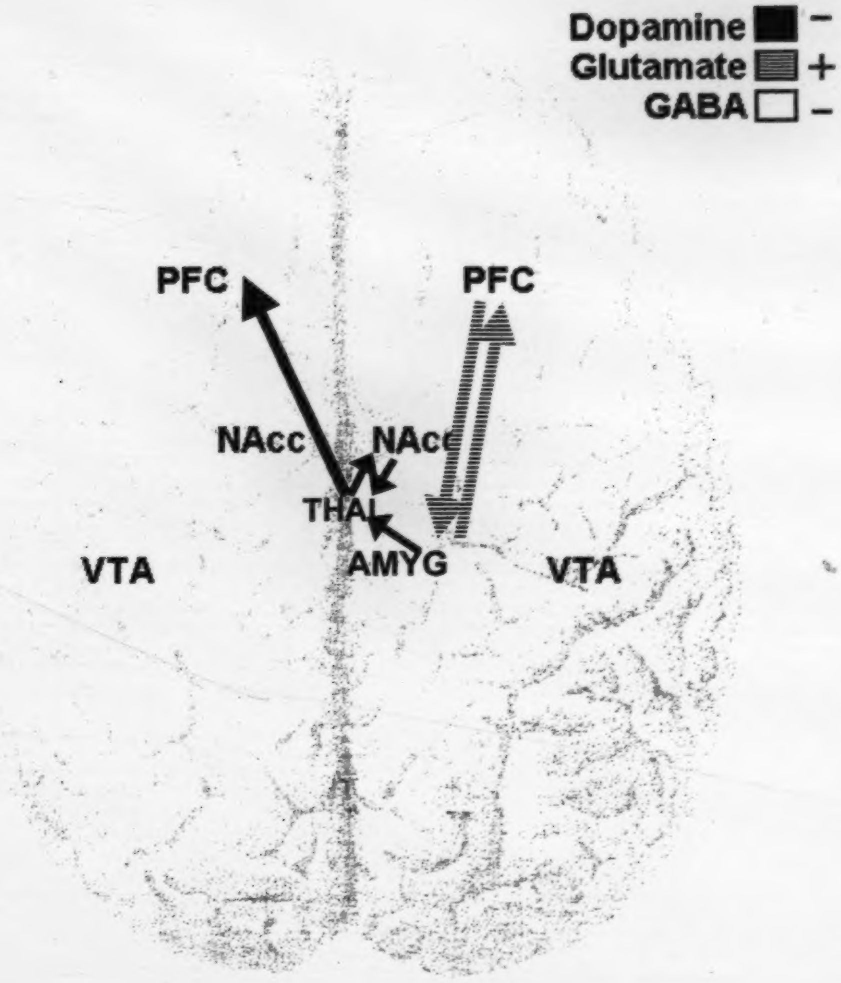

Dopamine ■ −
Glutamate ▤ +
GABA ☐ −
PFC
PFC
NAcc
NAcc
THAL
AMYG
VTA
VTA

Figure 3.4 Proposed neuroanatomical transmitter changes during *relapse*. Following a significant stressor, RH PFC function (which is already increased in abstinence) triggers activity in the right amygdala. The amygdala sends a signal to the mediodorsal nucleus of the thalamus, which projects bidirectionally with the NAcc in both hemispheres. The thalamus also projects to the PFC, resulting in increased LH cortical activity, and associated approach behaviour.

CHAPTER FOUR: CONSTRUCTION AND VALIDATION OF THE MULTIDIMENSIONAL MULTITRAIT CRAVING QUESTIONNAIRE (MMCQ)

Rationale for Questionnaire Construction

When considering the results of studies using different craving scales, it is important to consider the comparability of the measures utilized. This section is designed to provide an overview of some of the advantages and problems with existing instruments (detailed reviews can be found in Anton and Drobes, 1998; Mezinskis et al., 2001; Piazza et al., 2000; Potgeiter et al., 1999), and examine their comparability.

One problem with many craving measures is that they are mainly used clinically, rather than in research settings. Many investigators favour the use of simple, single-item or visual analog scales, with good face validity. They defend this technique claiming that researchers attempting to build more complex models have "needlessly complicated" the question under study, since "how many questions does one really need to ask smokers to establish how much they think they want to smoke a cigarette?" (Kozlowski et al., 1996). However, these screens fail to address questions of reliability and validity (Anton and Drobes, 1998; Kouimtsidis, 2000; Mezinskis et al., 2001; Tiffany and Carter, 1998). In fact, fewer than 10% of studies use a multi-item assessment or report on psychometric qualities such as instrument reliability (Carter and Tiffany, 1999). So, although a number of interesting dependence scales have been generated *ad hoc* to assess some dependent variable (see Voris et al., 1991), their psychometric properties are poorly documented.

Second, there are problems with this line of reasoning. While use of face valid questions appears sound, the main objective of screening tests is to maximize the number of individuals correctly ascertained as having a problem, while minimizing the number of false positives (Piazza et al., 2000). This problem is compounded in addiction, characterized by relatively high rates of denial and prevarication. When "logically-derived" face valid screens are used, there is a high propensity for individuals to "fake good". Conversely, "empirically-derived" screens may have good predictive validity, despite poor face or content validity (Piazza et al., 2000).

Third, a simple one-item scale may generate the same answer for two people, but closer scrutiny (e.g., regarding history of impulsive behaviour, obsessionality, other addictions, etc.) is likely to reveal qualitative differences, yielding a more complex understanding of the phenomenon. Some authors argue that cravings are not defined the same way, even among addicts for the same drug (e.g., whether craving refers to any urge to use, a strong urge, or something else entirely; Kozlowski et al., 1989). This is not to mention possible differences in craving between drugs. Further, Sinha and O'Malley (1999) point out that drug abusers, "differentiate between conscious thoughts about using and uncontrollable urges to use substances", making scores on one-item scales difficult to interpret. Finally, several predisposing factors, including cue exposure, actual ingestion, negative affect, and stress, appear instrumental in evoking craving (Sinha and O'Malley, 1999). Simple one-item scales cannot adequately measure the impact of these competing factors. Hence, while the use of short forms is understandable in clinical settings, it comes at the expense of reliability and comprehensibility.

Fourth, different time frames hinder comparability of various scales. Some scales ask questions regarding present feelings and urges, while others assess thoughts and feelings occurring in the past day, month, or year. To this end, Kouimtsidis (2000) has noted that craving scales asking the user to average their urges over a period of time may offer more reliable measures. On the other hand, Mezinskis and co-workers (2001) have argued that it may be difficult for subjects to reliably average cravings across time, and so use of a shorter time interval may increase predictive power.

Fifth, there may be issues specific to questionnaire construction. For instance, a factor analysis of Tiffany and Drobes' (1991) Questionnaire of Smoking Urges (QSU) yielded two factors that the authors argued represented positive and negative reinforcement. However, a reanalysis suggested that this finding was due to the presence of negatively-worded items which clustered together; these authors found evidence for three dimensions: intentions, urges, and expectancies (Kozlowski et al., 1996).

Sixth, existing questionnaires do not systematically evaluate cognitive, affective, and behavioural dimensions. As a result, most are biased in favour of one dimension or another, with little consideration regarding internal consistency. This is important, as some dimensions may be more important for some people than others, or their relative importance may shift over the drug use cycle (Anton and Drobes, 1998). For instance, in a comparison of different craving rating instruments, Potgeiter, Deckers, and Geerlings (1999) argued that each scale was measuring a different facet of alcohol craving: the Obsessive Compulsive Drinking Scale (Anton et al., 1995) is most concerned with *thoughts* about alcohol; the German Lubeck Craving Scale (Veltrup, 1994) measures *desires* for alcohol; and the Alcohol Craving Questionnaire (Singleton et al., 1995) is most tied to *expectations* regarding alcohol use. It was argued that, as a result, each of the scales missed essential information. Similarly, some questionnaires appear to index unrelated domains, (e.g., Voris et al., 1991), such as health and energy level. These inconsistencies are likely amplified when comparisons are attempted between questionnaires for different drugs. Both Potgeiter and co-workers (1999) and Tiffany (1990) argue that one multidimensional instrument is necessary to capture the multifaceted nature of the craving concept.

Finally, some well-constructed scales, which do ask questions regarding all three domains (e.g., the QSU; Tiffany and Drobes, 1991), or attempt to survey both internal and external triggers (e.g., the Minnesota Cocaine Craving Scale; Halikas et al., 1991), are constructed for the purpose of measuring cravings for one specific drug. This is partially because research on cravings for specific drugs is traditionally conducted by researchers working in relative isolation (Gossop, 1990). These problems decrease the generalizability of information obtained. Hence, while some authors have argued that cravings play a particularly strong role in certain drugs or drug classes, such as psychostimulants (Halikas et al., 1991), this remains speculative because most questionnaires do not actually assess cravings between drugs; hence, no existing assessment tool for measuring cravings for alcohol and cocaine was available.

Such issues are likely to become especially important in the future, given the number of novel pharmacological interventions designed around craving reduction.

A Novel Multidimensional Craving Scale: The MMCQ

Problems with comparability of different questionnaire measures, particularly comparing different substances, and their tendency to ignore the multidimensional nature of craving, led to the development of a novel craving questionnaire measure. Hence, the Multidimensional Multitrait Craving Questionnaire (MMCQ) was constructed for this thesis.

The MMCQ was developed for the purpose of creating a standardized testing instrument suitable for the measurement of cravings for different substances, as well as behaviours (i.e., in process addiction). Unlike the brief screens used clinically, this tool sought to examine details of the factor structure underlying craving. Although the construction of the final version requires more extensive testing and refinement, it was hoped that the data gathered in this thesis would function as an independent variable assessing craving in both alcohol and cocaine dependence, and serve as a prototype for a psychometrically-sound craving questionnaire for use in research.

The overall Flesch-Kincaid grade reading level of the questionnaire is 7.4. All items are worded so that higher scores represented more/worse cravings[11]. While this is, in some ways, a departure from standard psychological practices, there were two substantive reasons why this was necessary. First, since the educational attainment of substance abusers is often lower than average, clarity was a central issue. Introducing both positively- and negatively-worded questions (particularly on such a long test) might be confusing, or at least laborious, for this population.

Second, as previously noted, some evidence suggests that reverse-scored items may group together statistically (Kozlowski et al., 1996).

Questions were presented on a standard IBM-compatible personal computer. It was anticipated that use of a computerized protocol would lessen social desirability and demand effects, and decrease human error in terms of scoring responses. The subroutine automatically randomized questions in the presentation of each subcategory (except for the first group of questions, which was given in the same order to all subjects), to control for order effects.

The first screen provided an operational definition of "craving", to control for subjective interpretations of the concept:

> *"A craving is defined as ANY URGE OR DESIRE that is very insistent and difficult to ignore (not just a strong or overwhelming urge). People can have cravings for drugs, foods, or even behaviours that seem to have addictive qualities. The following questions are designed to learn more about* your *cravings".*

The second screen outlined for the subject which drug was the substance of interest (i.e., the individual's "primary drug", since most subjects were polydrug abusers), as well as the time frame the subject was to utilize:

> *"The following questions refer to your cravings regarding a given drug or behaviour in the past two weeks. Typically, these questions will refer to your drug of choice. If you have experienced cravings for several types of drugs or behaviours over this period and are unsure which one is the topic of this questionnaire, please discuss with the test administrator."*

In addition to the presentation of these instructions onscreen, information was also verbally presented to the subject, with elaboration as necessary.

Domains of Interest

In total, 129 items were presented to each subject. A full list of the items is found in Appendix A. Questions were grouped into four subscales, and each item had an affective, cognitive, and behavioural correlate (e.g., "how did you feel when…", "what did you think when…", "what did you do when…")

The *general descriptive* subscale of the MMCQ queried quality, intensity, duration, and frequency information, and frequency of cravings for other substances. This section was always presented first, with items administered in the same order. One possible use for this "short form" might be as a 15-item screen, given strong inter-correlations with the entire questionnaire. The next three categories, which surveyed the three dimensions of craving, were randomized in terms of order of category presentation (i.e., categories were randomized).

The *behavioural* items surveyed included changes in craving as a result of hunger, sleep deprivation, and engagement in risky or sensation seeking behaviour. It also queried responses and behaviours of others. Finally, this section examined behaviours related to quitting, abstinence, relapse, as well as the relationship between cravings and suicide attempts.

The *cognitions* screened by the MMCQ included questions regarding how cravings interfere with thinking on a day-to-day basis, automaticity of processing, distractibility, perseveration, and expectations surrounding use. It also asked questions regarding successful control of cravings, and surveyed cognitions related to drug use, such as responses to cues, schedule-induced cravings, and vigilance. Finally, it examined cognitive styles including doubt surrounding one's ability to stay clean, ambivalence surrounding use, obsessiveness and perfectionism, stubbornness, and impetuousness.

In terms of *affective* variables, negative affective traits such as irritability, disgust, paranoia, shame, doubt and insecurity, anxiety and social anxiety, fear, depression distress, and feelings of suicidal ideation were examined. Positive affect questions mainly centred around camaraderie, in order to examine the role of "peer-influence" motivations for use. As well, it surveyed frontal lobe traits such as affective flatness and inappropriateness, boredom, ambivalence, and anhedonia.

A *total score* was calculated as the mean of these three dimensions. This was the score used for most statistical analyses, unless otherwise indicated.

Procedure

The subject was seated in front of a computer monitor, and instructions were read aloud with clarification as required. Explanation in the use of the mouse was given (when necessary), and the first question was presented as an example of how to record one's responses. Subjects were shown how to respond to each question by moving the slider between the anchors for each visual analog question using the computer mouse. The response to each question was automatically translated into a score from 0-100; scores were automatically saved as a Microsoft Excel-compatible text file.

Subjects were instructed to answer questions regarding their cravings in the past two weeks. This time scale increased comparability of this measure with concurrent measures of depression, anxiety, and impulsivity (see Chapter 7).

Before starting, subjects were told that 4 groups of questions (i.e., the general descriptive questions and the 3 categories) would be administered, and would be notified on the screen when each category of questions was about to begin.

For clarity, a computerized still image of a typical question is presented in Figure 4.1.

Participants

Subjects were recruited from the Henwood Treatment Centre, a residential inpatient rehabilitation programme neighbouring Alberta Hospital Edmonton (AHE) where the experiment was carried out in the Clinical Diagnostics and Research Centre (CDRC). The study was approved by the ethics committee at AHE, as well as by the director of admissions at Henwood.

All subjects signed forms indicating informed consent. Recruitment was restricted to males 18 years and older, who confirmed having cravings specifically for alcohol or cocaine[12]. All subjects fulfilled *DSM-IV* criteria for substance dependence.

There were several reasons for our decision to limit participation to males. Females exhibit a different pattern of vulnerability, including age of onset and familial pattern of inheritance as males (i.e., "primary" *vs.* "secondary" alcoholism; Wiers et al., 1994), and may show different affective reactions over the course of the addiction (Selzer et al., 1979). Differences associated with hormonal fluctuations have been documented in terms of both level of craving (e.g., Evans et al., 1999; Mannucci et al., 1998), stress level, and drug response (West and Michael, 1988). Relatedly, females exhibit a different pattern of scores for novelty seeking, harm avoidance (Van Gestel et al., 2002) anxiety (Compton et al., 2000) and impulsivity (Linnoila and Virkkunen, 1992) than males, and different neuroendocrine markers for many of these traits (Hansenne et al., 2002). Not surprisingly, different psychophysiological (e.g., Hill and Steinhauer, 1993; Johnston and Wang, 1991) and fMRI (Tapert et al., 2003) results of male and female drug abusers have been obtained. This may be because sex hormones play an important role in brain lateralization (Harris et al., 1996), resulting in different patterns of brain organization and different susceptibilities to lateralized damage (Flor-Henry, 1986). As a result, some researchers have concluded that relationships with drug use variables should, in general, be computed separately for the sexes (Hansenne et al., 2002). In addition, the majority of animal research focuses on males, as do most human studies of addictive behaviour. Finally, in practical terms, the lower proportion of female cocaine addicts in treatment would make it difficult to acquire the required sample size in a reasonable period of time.

As discussed above, within the alcohol and cocaine groups, comparisons were made between those with low, medium, and high cravings. We elected to use addicts as their own controls because of the difficulties associated with the measurement of cravings in normal controls. Aside from likely socioeconomic differences between the control and experimental group (Patkar et al., 2002), most controls have likely never experimented with hard drugs such as cocaine. Furthermore, use of a control group when examining a stigmatized behaviour is notoriously difficult, with individuals showing a tendency to normalize marginal behaviours; confirmation of any illicit drug use would require urine or blood samples which could decrease willingness to participate, or result in a non-representative sample. Another obvious problem was the choice for an appropriate substance for the measurement of cravings in the control group. Although some innocuous, commonly-used substances were considered (e.g., caffeine, or chocolate, or nicotine)[13], these substances may not generate cravings in all subjects, potentially creating a floor effect in measurement. Conversely, if some controls reported strong cravings for one of these substances, it would complicate their function *as controls* (i.e. they would, in effect, represent another craving group). Even if craving scores for the innocuous substance were low, ruling out other aspects of an "addictive personality" would still be problematic, since compulsive disorders can present with a wide array of phenotypes besides drug or alcohol use (Blum et al., 1994). Moreover, individuals in this group might in fact be more vulnerable to substance use disorders, and therefore represent false negatives. In addition, the majority of addicts in the study also use these substances, with the vast majority being current smokers (n = 51). Thus, use of this strategy might necessitate measurement of cravings for *the control substance* in the experimental groups. This would further create problems should any of the experimental group have stronger cravings for the innocuous substance than their drug of choice. And, at the same time, there are ethical surrounding asking newly abstinent addicts to refrain from nicotine or caffeine, a request that is generally not problematic in control populations.

This kind of problem is evident in previous studies of craving. Some studies have failed to treat control and experimental groups equivalently - for example informing the substance abuse group that during some sessions they should expect cocaine while the volunteer controls knew to expect placebo (Stapleton et al., 1995). By the same token, Knoblich and colleagues (1992) found a significant correlation between cocaine craving (frequency of pleasant thoughts) and cerebrospinal homovanillic acid (HVA) levels. However, these levels did not significantly differ from those found in controls, for whom no index of craving was available. For these reasons, we elected to use addicts as their own controls, comparing high *vs.* low levels of craving.

Overall, 54 individuals agreed to participate in the study, of which all completed the MMCQ. Subjects had just completed their second week of treatment. Each subject completed all testing in one session of 3.5h (approximate range 2.5-5h), which took place on either a Saturday or Sunday during the individual's weekend pass from Henwood. All neuropsychological tests, questionnaire measures, and electrophysiological tests were conducted by the author. Subjects were paid $10.00 for participation.

Demographic Characteristics. Of the original group of 54 subjects, 2 were ultimately excluded for medical reasons (one history of sporadic epileptic episodes, possibly associated with drug use; one history of multiple traumatic brain injury (TBI)), and 1 more was excluded for low reading skills (~ grade 6 reading level), precluding an understanding of the MMCQ. Individuals who did not meet criteria were informed and debriefed, thanked for their time, paid in full, and returned to the treatment centre.

Thus, for the neuropsychological and questionnaire measures (some were ultimately excluded from ERP analysis, as detailed in the following chapter), data was available from a total of 51 subjects, although *n*'s on some measures are smaller due to time constraints on the part of some subjects. 26 of these individuals were in the alcohol group and 25 were in the cocaine group; a full comparison of the results for these groups is provided in Table 4.1.

Overall, the subjects had a mean (SD) age of 37.4 (10.2), and had completed an average of 10.2 (6.8) years of education. 92.2% were right handed although 40.0% had a positive family history of left handedness among first degree relatives, and over ¾ of right handers (37/47) were classified as inconsistent or mixed handedness. These observations, again, point to the increased susceptibility of left-handers to addictive tendencies, given the partially-genetic basis of handedness (Coren, 1992). Independent *t*-tests revealed no significant differences between the alcohol and cocaine groups in terms of these demographic variables.

Alcoholics had a significantly longer history of use than cocaine users (19.4 *vs.* 10.2 years; t=3.30, $p < 0.01$), but did not differ in terms of their frequency of use (20.5 *vs.* 20.3 each month [28 days]), self-reported relapses (7.3 *vs.* 5.5), or days clean (37.1 *vs.* 39.4 days). The longer use history of alcoholics is likely due to the legal nature of the substance, its greater availability, and the lower social stigma associated with its use. This interpretation is supported by their marginally lower age of first use (20.0 *vs.* 25.2 years of age). Importantly, their scores on the Problem Use Scale did not differ significantly (66.9 *vs.* 72.9), nor did they differ on any subscale of the MMCQ. In fact, there was no difference in the number of alcoholics or cocaine addicts in the low, medium, or high craving groups ($\chi^2 = 0.64, p > .7$). Since neither demographic variables nor dependence severity differed between the two groups, and because previous ERP studies of cocaine and alcohol found either similar amplitude decrements in these groups (Bauer, 2001) or no additional effects of alcohol exposure upon cocaine-related effects (Biggins et al., 1997), the groups were collapsed for analyses of electrophysiological, neuropsychological and questionnaire data.

Wherever possible, pairwise deletion was applied to missing values. This was done in case subjects with some common characteristic systematically chose not to answer the same questions, resulting in the possible exclusion of a potentially meaningful subclass of individuals (e.g., listwise deletion of subjects refusing to answer a personal item might generate a bias in keeping responses only from those subjects with lower regard for social conventions, a theoretically important variable). Listwise deletions were performed when pairwise deletions resulted in the inability of SPSS to perform matrix calculations (typically in principal components factor analytic situations). Where applicable, listwise deletions are noted in the text.

Results

It has been noted that any instrument attempting to assess a clinical construct must possess the following psychometric characteristics (Kampman et al., 1998): (1) Good interrater reliability; (2) acceptable internal consistency; (3) concurrent validity, via agreement with other known measures of the same or similar constructs; (4) discriminative validity, in terms of differentiating the target group from other groups; (5) good predictive validity; (6) good face validity. An analysis of these characteristics, as they pertain to the MMCQ, is discussed below.

Interrater Reliability. This was not applicable, as the MMCQ is computer scored.

Internal Consistency. Examining all 129 items concurrently (listwise $n = 28$) revealed a standardized Cronbach's α of .969, suggesting very strong internal consistency.

Concurrent Validity. Concurrent validity was assessed by examining the correlation between the MMCQ and Curran et al.'s (1997) Problem Use Scale. The Pearson correlation between these two questionnaires was relatively strong ($r = 0.497$, $p < .001$). In addition, the three subscales and the general descriptive questions themselves correlated highly with problem use (all p's $< .001$). These and discriminant validity results are presented in Table 4.2 (non-parametric comparisons where applicable, as indicated by Levene's test for equality of variances).

It is of interest to note that, while the correlation between the MMCQ and the Problem Use Scale was relatively strong, the two questionnaires cannot be considered interchangeable, nor do they measure the same constructs. The MMCQ deals with symptoms of dependence, whereas the Problem Use Scale indexes behavioural and social difficulties encountered (e.g., with the police, family, or an employer) as a result of excessive drug use.

Discriminant Validity. It was hypothesized that the MMCQ would discriminate between heavy- and light-users within a dependent population. As such, we predicted correlations between the MMCQ and variables such as drinking frequency, duration of substance use, the number of criteria met for dependence, and self-reported relapses.

Surprisingly, few correlations were noted with these variables, except that the affect subscale correlated with both drinking frequency ($r = -0.315$, $p < .05$). A marginal correlation was also seen with self-reported relapses ($r = 0.278$, $p < .06$). Note, however, that these correlations were in opposite directions. While these results were unforeseen, they are in line with observations that craving does not appear to predict drug use behaviour. They may also reflect the fact that the MMCQ surveyed cravings in the last two weeks, during which time all the subjects in this study were actively undergoing rehabilitation.

Predictive Validity. At present, the predictive validity of the MMCQ remains unknown. Ultimately, use of this tool as a predictor of relapse might be a reasonable goal. However, because this population is notoriously transient, it proved difficult to retest them at a later date. Other areas of future investigation may examine correlations between this measure and behavioural changes over the course of treatment, or differences in treatment retention rates.

Face Validity. Face validity was assessed informally; subjects were queried after completing the questionnaire as to whether questions had relevance to their daily lives.

Virtually all subjects reported strong relevance to their experiences with their drug of choice. Of note, three subjects reported actually experiencing cravings while completing the instrument, and two cocaine-using subjects reported cocaine "use dreams" the night following testing (although, this could also have been due to other aspects of the testing session).

One subject reported difficulty understanding some of the questions, presumably on account of the fact that English was not his native language. Informally, a strong relationship was noted between reading speed (as observed during the course of testing) and time required to complete the MMCQ; while the questionnaire took half an hour on average, a couple of slower readers required almost an hour. Since the time required to complete the measure might vary systematically with other testing variables, such as frustration and cooperation, one important consideration for future use of the instrument is reduction in the number of items, or possible rewording of questions to further decrease reading level.

Factor Structure of the MMCQ. Principal components analysis (PCA) using varimax rotation was performed to analyze the underlying factor structure of the questionnaire. Listwise deletion of missing data was employed, as pairwise deletion resulted in a matrix that was not positive definite.

It was hypothesized that three factors (underlying the cognitive, affective, and behavioural dimensions) would emerge. Contrary to this expectation, one factor emerged as the strongest, explaining almost a quarter (24.6%) of the total observed variance. 26 factors met Kaiser's (1960) criteria, with eigenvalues greater than 1.0, cumulatively explaining 99.4% of the variance. However, using Cattell's scree plot criteria (see Figure 4.2), only 8 factors, accounting for 64.8% of the variance, appeared large enough to warrant consideration. A full description of these factors, and their postulated conceptual meanings, is presented in Table 4.3, with accompanying rotated factor loadings for the items presented in Table 4.4. To examine the internal consistency of scales comprised of these factor items, Cronbach's α's of the subscales were also calculated, and were found to be in the range of 0.77 - 0.95.

As mentioned above, the first factor of the MMCQ, one that could be described as craving intensity, accounted for approximately ¼ of the total variance. The 2nd factor was generally associated with troubling cognitions. Conversely, the 3rd factor was more related to sensation seeking and positive aspects of drug use. The 4th and 5th factors appeared to be related to poor self-esteem and suicidal ideation, respectively; obviously, these factors could be of clinical concern in the overall assessment of cravings. The 6th factor appeared to be related to schedule-induced aspects of craving (e.g., time- and place-related effects), as well as cravings associated with boredom and "having nothing to do". The 7th factor was associated with craving for drugs as a coping mechanism. Finally, the 8^{th} factor appeared to assess anxiety and related constructs, such as "surprisingness" and urgency of cravings.

Although no correlation was noted between craving and days clean (see Table 4.2), it was of interest to see whether the pattern of factor scores differed between those in early withdrawal compared to those who had been abstinent longer, as predicted by our model. A closer examination of the factor scores in individuals in early withdrawal (mean 20.7 days; SD 3.9; range 14-27 days) *vs.* later abstinence (mean 52.6 days; SD 21.9; range 28-105 days) demonstrated that subjects did in fact have a different pattern of factor scores in the two groups. For brevity, only the first 5 factors for the two groups (explaining 65.5% and 69.5% of the total variance, respectively) will be discussed below.

For subjects in early withdrawal, the first factor was actually a composite of factors 9 and 10 in the overall group (early morning cravings and a dependent self-concept, respectively). Early morning cravings are thought to be a strong indicator of withdrawal, and are included in most dependence screening questionnaires (e.g., see review by Piazza et al., 2000). The second factor in this group was, as predicted by the model, factor 8, restlessness, urgency, and impulsiveness. The third factor in this group was distressing cognition, while the 4th most closely resembled schedule-induced craving. Surprisingly, craving intensity, which was the most prominent factor in the total group, was factor 5 amongst those in early withdrawal, explaining only 8.1% of the variance in this group. This pattern of factor scores suggests that cravings in early withdrawal are characterized by withdrawal symptoms, significant distress and anxiety, and a tendency to view oneself as addicted. As predicted by the model, conscious intensity of craving does not appear to be a significant component of craving in early withdrawal.

Among late withdrawal subjects, the pattern was quite different. Craving intensity explained the most variance in this group. The second factor did not appear to correspond to any factor in the total group, but was comprised of elements of schedule-induced craving, and anxiety/distress. The third factor resembled both the low self-esteem, and social factors in the original analysis. The fourth factor resembled the coping mechanism factor and the distressing cognition factors, while the fifth factor related most closely to suicidal ideation and sensation seeking. In other words, the pattern of factor scores for this group appeared to be driven most strongly by craving intensity, but was also characterized by distressing cognitions, poor self-esteem, approval seeking and suicidal ideation. Clearly, at least among newly abstinent males, the nature of craving changes significantly over time.

Discussion

Overall, the MMCQ demonstrated very high internal consistency, and good concurrent validity with the Problem Use Scale (Curran et al., 1997). Face validity, informally assessed, appeared good, but suggested that structured assessment of cravings may actually trigger the craving process *per se.* Concurrent validity was lower than face validity, but this may not be surprising given the fact that craving is not considered a good predictor of relapse, and the fact that subjects were asked about craving during a time when all were in imposed abstinence.

Surprisingly, no differences were found between alcohol and cocaine craving, either on the total or subscale scores. This is in agreement with other studies reporting comparable craving intensity levels for cocaine and alcohol (Mezinskis et al., 1998), contradicting conventional reasoning that cravings are most severe for psychostimulant drugs (Halikas et al., 1991).

A principal components factor analysis of the items yielded 8 factors, accounting for approximately two-thirds of the overall variance of the questionnaire. Several factors were of potential clinical relevance. Suicidal ideation, related to lowered serotonin levels (Linnoila and Virkkunen, 1992) was a factor in the craving scores of the late but not early withdrawal subjects, as predicted by our model. The strongest factor, craving intensity, accounted for approximately one-quarter of the total variance. In this regard, it is noteworthy that Halikas and co-workers (1991) found craving intensity to be the only significant predictor of cocaine abstinence. The 8th factor, which assessed pertained to cravings that occurred "out of the blue", a sense of urgency, and physical symptoms of anxiety, accounted for little of the overall variance (~4%), yet had very high internal consistency (α = .90). It also played a stronger role in early withdrawal than in long-term abstinence. Speculatively, this factor could be associated with left hemisphere activation.

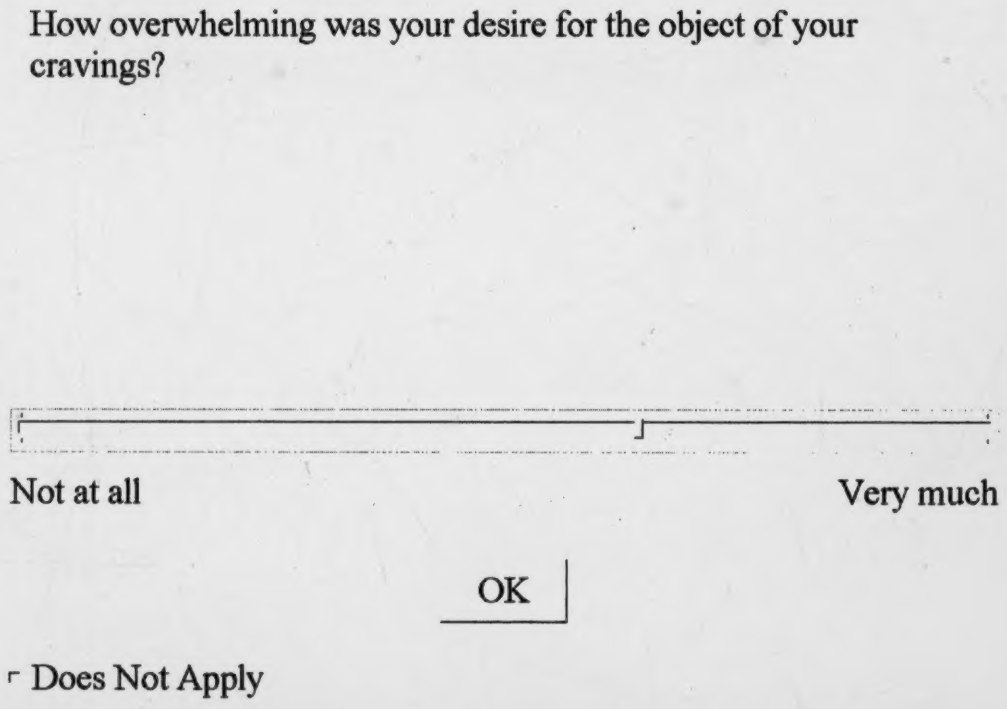
This factor analysis substantiates the notion that a brief, single item assessment of craving is unlikely to capture the multidimensional nature of the construct. Further, a comparison of newly abstinent and later abstinent subjects suggests that the pattern of factor scores shifts over time, with classical signs of withdrawal more central to cravings described by the early withdrawal subjects, and craving intensity more important among the late withdrawal subjects.. This appears to be a novel finding.

Summary

While the MMCQ clearly requires more extensive testing, these pilot results demonstrate that it has excellent internal consistency and construct validity. Concurrent validity, assessed using an independent questionnaire of problem drug use, was also high. These results suggest that its use as the independent variable in this thesis is justified.

The number of independent factors derived from a principal components analysis of the MMCQ supports the contention that craving is multidimensional, and more complex than can be understood with a one-item visual analogue scale, as is commonly utilized. Although the factors did not map onto the affective, cognitive, behavioural construct set predicted by the author, they nonetheless provide justification for the use of more complex craving measures in research. Moreover, the factor structure may shift over time. The factors include areas conceptually linked with craving, such as sensation seeking, distressing cognitions, and low self-esteem. Of particular note clinically was the finding of a suicidal ideation factor associated with craving. These findings suggest that craving measurement in treatment settings may have important consequences beyond the scope of drug use. These findings call for independent work to substantiate the factor structure of craving.

Future work with this questionnaire intends to examine content validity, via detailed item assessment by expert raters in the field of addiction. Larger *n*'s are required, as are individuals with different types of drug dependence. To examine discriminative validity normal controls will also be surveyed. Further, more systematic investigation into changes in the factor structure of craving over the course of the drug cycle is intended. Finally, the predictive validity of this measure warrants future study.



How overwhelming was your desire for the object of your cravings?

Figure 4.1 Still image of an MMCQ item. The image as presented fills the entire screen. The subject moves the slider along the horizontal line to indicate his response. Each item is automatically scored (0-100), and exported into a Microsoft Excel® file, where scales and subscales can be calculated. Software © 2000 by J.D. Robinson, for Salience Products and Consulting Group.

Measure	**Group Mean (*n*=51)**	**Alcohol (*n*=26)**	**Cocaine (*n*=25)**	***t*-score**
Demographic Variables				
Age	37.41 (10.23)	39.38 (10.66)	35.36 (9.56)	1.42
Age of drug use onset				
(drug of choice)	22.52 (10.28)	19.98 (11.40)	25.16 (8.40)	-1.84†
Education	10.18 (6.83)	9.35 (8.41)	11.04 (4.69)	-0.89
Handedness				
(Annett)	2.31 (1.09)	2.42 (1.06)	2.20 (1.12)	0.73
(Chapman)	15.18 (5.80)	15.58 (5.38)	14.76 (6.30)	0.50
Drug Use Variables				
Problem use scale	14.89 (10.98)	66.92 (16.46)	72.92 (14.60)	-1.37
Frequency of use				
(monthly)	20.41 (9.44)	20.54 (9.64)	20.27 (9.44)	0.10
Years of substance use	14.89 (10.98)	19.40 (12.15)	10.20 (7.23)	**3.30****
Days clean	38.24 (22.86)	37.08 (22.05)	39.44 (24.07)	-0.37
Number of self-				
reported relapses	6.41 (10.37)	7.29 (10.38)	5.52 (10.50)	0.59
MMCQ Measures				0.67
Total Score	59.70 (14.39)	61.04 (10.89)	58.31 (17.43)	
General descriptive				-0.27
information	62.34 (19.26)	61.63 (19.87)	63.08 (18.97)	
Behaviour subscale	52.57 (15.69)	54.36 (13.13)	50.71 (18.06)	0.83
Cognition subscale	62.30 (14.26)	62.52 (9.47)	62.08 (18.16)	0.11
Emotion subscale	64.23 (17.16)	66.25 (14.41)	62.13 (19.71)	0.85

†Mean difference marginally significant ($.05 < p < .09$)
*Mean difference significant at the 0.05 level (2-tailed)
**Mean difference significant at the 0.01 level (2-tailed)

Table 4.1 Comparison of the alcohol and cocaine groups: Demographic and drug use variables (presented as mean (SD)).

Measure	**MMCQ Total Score**	**General Descriptive Information**	**Behaviour Subscale**	**Cognition Subscale**	**Emotion Subscale**
Problem use scale	**.497****	**.384****	**.523****	**.437****	**.409****
Frequency of use (monthly)	-.213	.041	-.091	-.167	**-.315***
Years of substance use	-.054	-.167	-.056	-.061	-.035
Criteria met for dependence	.175	.253	.183	.150	.149
Days clean	-.065	.005	-.095	-.072	-.017
Number of self-reported relapses	.206	.113	.138	.139	.278†

†Correlation marginally significant ($.05 < p < .09$)
*Correlation is significant at the 0.05 level
**Correlation is significant at the 0.01 level

Table 4.2 Correlations between the MMCQ and drug use variables.

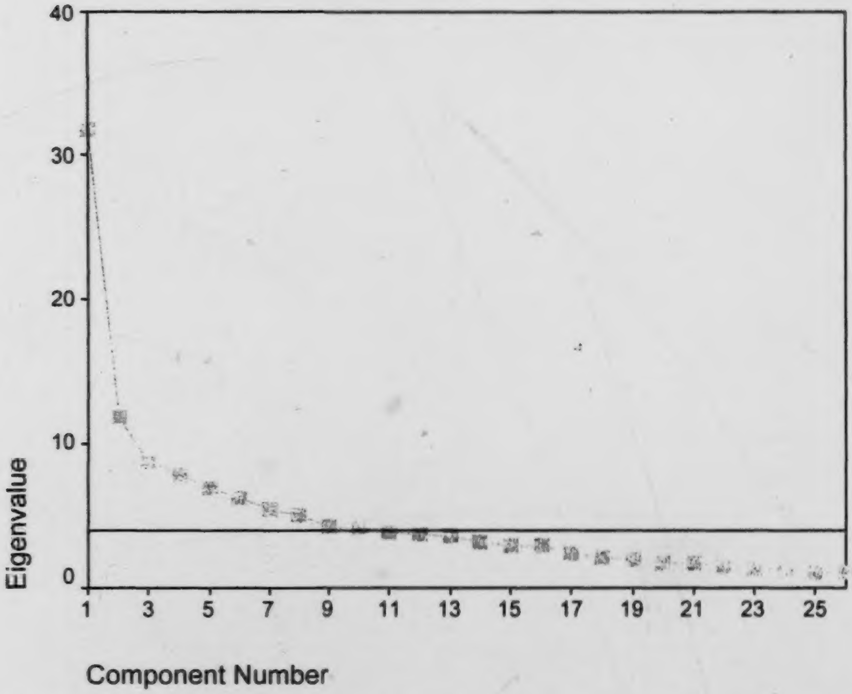


Figure 4.2 Scree plot suggesting use of 8 factors in the principal components analysis.

Factor	Conceptual Meaning	Eigenvalue	Total %Variance Explained	Cumulative Total % Variance	Total Items	Cronbach's α - subscale (Listwise *n*)
1	Craving intensity	31.74	24.61	24.61	21	.952 (41)
2	Distressing cognitions	11.82	9.16	33.77	16	.916 (43)
3	Social/ sensation seeking	8.78	6.81	40.58	13	.876 (43)
4	Low self-esteem	7.78	6.03	46.61	7	.835 (45)
5	Suicidal ideation	6.90	5.35	51.95	6	.847 (38)
6	Schedule-induced; boredom	6.16	4.78	56.73	8	.777 (44)
7	Coping mechanism for other pressures	5.38	4.17	60.90	4	.769 (45)
8	Anxiety, restlessness, urgency	4.99	3.87	64.77	7	.896 (49)

Table 4.3 Factors derived from a principal components analysis of the MMCQ (Listwise *n* = 28).

Rotated Component Matrix

	1	2	3	4	5	6	7	8
How often did you find yourself thinking about the craved object or behaviour?	.937							
How often did you have a craving for the object or behaviour?	.920							
How long did you spend thinking about the craved object or behaviour at any given time?	.899							
How intense were your cravings?	.853							
How long did your average craving usually last if it could not be satisfied?	.828							
How demanding were your thoughts about the object of your cravings?	.816							
How much did thoughts about the substance or behaviour distract you from other thoughts?	.765							
How overwhelming was your desire for the object of your cravings?	.749							
How obsessive or recurrent were your thoughts about the object of your cravings?	.733							
How likely were you to convince yourself you had to satisfy the craving "this minute"?	.695							
How likely were you to constantly desire the object of your cravings?	.660							
How powerless did you feel about quitting?	.652							
How likely were you to constantly obsess about the object of your cravings?	.625							
How likely were you to check for access or availability to what you craved?	.610							
How likely were others to avoid spending time with you because of your cravings?	.604							
How compulsive was your use of the substance, or the performance of the behaviour?	.518							

How likely was having to sneak around or be secretive to lead to cravings?	.493							
How much time did you "keep busy", fighting your average craving?	.487							
How likely were you to constantly return to the source of your cravings?	.485							
How likely were you to justify to yourself why it would be okay to indulge in your cravings?	.471							
How likely was a preoccupation with details to lead to cravings?	.441							
How likely were you to have cravings when you were feeling doubtful or insecure?		.876						
How likely were worries about problems, and thoughts that made your mind race, to lead to cravings?		.744						
How likely were thoughts about things that scare you to lead to cravings?		.727						
How likely was having an argument with someone to lead to cravings?		.723						
How likely was doing things that made you cry or feel exhausted to lead to cravings?		.698						
How likely was second-guessing your decisions or actions to lead to cravings?		.689						
How likely was seeing friends using the substance or behaviour to lead to cravings?		.571						
How likely was doing something you'd expected to enjoy, but found you did not, to lead to cravings?		.568						
How likely were thoughts about not feeling as much as you were "supposed" to feel to lead to cravings?		.565	.422					
How likely were thoughts about how slow and difficult it is to get things done to lead to cravings?		.522						
How likely were thoughts about things you felt guilty for or should have done to lead to cravings?		.507						.460
How likely were suspicions about others plotting against you to lead to cravings?	.405	.496						
How difficult was it to think clearly around the time of day you were used to having what you craved?	.416	.469						
How likely were doing frightening		.455						

things to lead to cravings?				
How likely were you to get emotional around the time of day you were used to having what you craved?	.455			
How likely were you to have cravings when you were feeling uncomfortable being with others?	.419			
How likely were you to use the substance or perform the behaviour because you felt peer pressure?		.871		
How excited were you by the thought of reaching a "shared high" with friends?		.768		
How likely was curiosity about new things to lead to cravings?		.705		
How difficult was it to keep from replaying the memory of indulging in your mind?		.669		
How much did others support or encourage you to use the craved substance or behaviour?		.644		
How likely were you to use the object of your cravings when you were reminded of it?		.604		
How much were cravings brought on by thoughts about having to "fit in" with the crowd?		.599		
How likely was the excitement of an "adrenaline high" to lead to cravings?		.593		
How likely were attempts to clean, organize, or "fix" your environment to lead to cravings?		.577		
How likely were you to spend time planning ways to share your craved substance or behaviour with others?		.532		.434
How likely was trying to do things just to meet other people's standards to lead to cravings?	.476	.530		
How likely was taking part in "fun" activities but feeling nothing to lead to cravings?		.501		
How likely was doing things you knew you shouldn't be to lead to cravings?		.492		
How likely were you to have cravings when you were feeling ashamed or guilty?			.921	
How likely were you to have cravings when you were feeling worthless and that life was not worth living?			.870	

How likely were you to have cravings when you were feeling disgusted with yourself or others?				.681		
How likely were you to have cravings when you were feeling depressed or sad?				.673		
How likely were you to have cravings when loved ones were making you feel resentful?				.645		.496
How likely were you to have cravings when your mind was sluggish or disoriented due to lack of sleep?				.635		
How likely were you to have other cravings (e.g. for food, cigarettes, sex, alcohol, or other drugs)?				.598		
How much did your cravings make you seriously think about ending your own life?					.923	
How much did your cravings make you feel sad or upset enough to want to end your own life?					.822	
How likely were your cravings to be the cause of attempting suicide?					.733	
How likely were plans or daydreams about ways in which to end your life to lead to cravings?					.698	
How likely were suicide attempts to lead to cravings?					.621	
How likely were you to act cautiously when others were indulging their cravings?					.477	
How likely were you to give in to your cravings around the time of day you were used to having what you craved?						.832
How often did you use the craved substance or perform the craved behaviour?						.706
How much did attempts to use the substance or perform the behaviour get in the way of other things you had to do?						.598
How much were your cravings based on expectations of how good it would feel?						.566
How likely were you to use the substance or perform the behaviour just to have something to do?						.515
How likely was your behaviour to be impulsive when you were craving?	.454		.406			.512

How much did you think about these other substances or behaviours?				.401		-.471		
How likely were you to have cravings when you were feeling bored?				.401		.470		.418
How likely were you to crave the substance or behaviour when all you could think about was getting food?							.816	
How upset did you feel about having to avoid the substance or behaviour?							.692	
How much of a "rush" did you get out of using the object of your cravings?							.627	
How emotional did you become when something reminded you of what you craved?	.433						.461	
How likely were you to have cravings when you were feeling annoyed or irritated?								.626
How much were cravings brought on by thoughts about having a good time with those around you?								.621
How likely was doing things that made your heart pound, your palms sweat, or otherwise made you jittery and tense, to lead to cravings?				.418				.538
How likely was restlessness and an urgent craving to overwhelm you?	.493							.529
How likely were you to find yourself thinking about the substance or behaviour "out of the blue"?								.472
How likely were you to have cravings when you were feeling anxious, distressed, or uneasy?		.466				.456		.468
How likely were thoughts about things that "bugged you" or got on your nerves to lead to cravings?		.418		.417				.451

Table 4.4 Rotated factor matrix of the first 8 factors of the MMCQ (Listwise *n* = 28).

CHAPTER FIVE: ELECTROPHYSIOLOGY

Rationale

One promising area in the search for possible markers of dependence is the event-related potential (ERP). ERPs represent the average electroencephalographic activity occurring in response to some event, whether external or internal. Averaging a number of individual responses enhances the signal-to-noise ratio, allowing activity time-locked to the stimulus to be observed. ERPs are comprised of a number of underlying waveform components, thought to represent specific information processing activities which occur in the brain in response to an eliciting event, as a function of task demands (Donchin et al., 1997). Multi-subject averaging is typically employed in order to further reduce variance attributable to differences between individuals. Hence, group comparisons can be made regarding the amplitude or latency of a given component.

Components are often sorted into early (<200ms) vs. late, with earlier components mainly reflecting the physical properties of the stimulus while later ones are indicative of cognitive processing. Typically, the waveform of interest in studies of vulnerability, drug abuse, and dependence is the P300 or P3b (see next section). This positive deflection, occurring roughly 300-600ms post-stimulus, is characteristic of the “oddball” task, in which rare stimuli are interspersed with frequent ones. The rare stimuli elicit the P3b, which is generally thought to index “context updating” of working memory (Donchin, 1981; Donchin et al., 1997), that is, it provides a real-time manifestation of a hypothetical internal “executive control system” responsible for deviance detection (Donchin et al., 1997). Hence, the context-updating model argues that the P3b is elicited when unanticipated (i.e., rare) events update the current working model of the environment.

Amplitude of this waveform appears to be proportional to task relevance, resource allocation, and inversely proportional to the subjective probability of the eliciting stimulus; that is, it is "proportional to the amount of change required in the model" (Donchin et al., 1997). A number of studies, outlined below, document systematic changes in the amplitude of the P3b waveform associated with addiction.

ERPs have several qualities making them valuable for the study of substance abuse. They have good test-retest reliability in both normal and patient groups (Sinha et al., 1992), and show heritability in families (Steinhauer et al., 1987), suggesting their potential as a genetic trait marker. They appear to be sensitive to both predisposing factors and current use; waveform amplitude is predictive of substance use disorders (Berman et al., 1993; Iacono, 1998), discriminates between users and nonusers (Hill et al., 1995; results for the N250 but *not* the P300), and measures length of abstinence (Bauer, 2001). It also appears to be sensitive to personality variables related to drug use, such as the Disinhibition subscale of sensation seeking (Zuckerman, 1990), and separate waveforms may be sensitive to different aspects of emotional processing (Vanderploeg et al., 1987). ERPs also meet the prerequisite conditions for studying affective and cognitive processes, in that they are noninvasive, enable comparison of different mental states, and have high temporal resolution with the potential for various *post hoc* extractions (Davidson, 1992). Further, as is also the case with emotional responses (Laurian et al., 1991), event-related potentials are particularly suited for the study of craving because the phenomenon is subjective and relatively brief in duration. However, we contend that the study of craving should directly examine proposed areas of cognitive deficiency, rather than employ the commonly-used oddball paradigm.

The P3b Waveform in Addiction

Most research in the area of substance abuse has focused almost entirely on the auditory oddball paradigm and irregularities in amplitude or latency of the P3b waveform component. This component is thought to be sensitive to both subjective probability and stimulus meaning (Johnson, 1993). The precise cognitive processes subserved by the P3b are still under dispute, but generally it is thought to be related to the cognitive evaluation of stimuli (Berman et al., 1993), or, more generally, the individual's capacity to process stimulus information (Hill et al., 1995). As noted above, many argue that it indexes "context updating" (Donchin, 1981; Donchin et al., 1997; Knight and Scabini, 1998; Verleger et al., 1994), in the context of the oddball paradigm.

The genetic basis of the P3b component was established in a comparison of monozygotic and dizygotic twins using a modified oddball task (Katsanis et al., 1997). The authors found 79% of the variance in P3b amplitude to be genetically determined, with monozygotic twins as similar to their co-twin as to themselves. This high degree of heritability may particularly hold true in addiction. Hill et al. (1999) demonstrated that parent-offspring transmission of P3b amplitude is greater in high- addiction risk than low-risk families (40% *vs*. 29%, respectively)[14]. Some authors have suggested that the reduced amplitudes of the P3b found in vulnerable individuals may represent a phenotypic expression of the DRD2 A1 allele (Berman et al., 1993, although see Blum et al., 1994), which is related to both novelty seeking (Bardo et al., 1996) and drug use (Berman et al., 2002).

Several studies have examined the predictive power of P3b amplitude in vulnerable individuals (i.e., in probands with alcoholic first degree relatives). Carlson and co-workers (unpublished manuscript, 1998; as described in Iacono, 1998) found that, of postpubertal males with large P3b amplitudes, none had a substance use diagnosis, while over 30% of those with the lowest amplitudes did. This measure was also useful in predicting who would develop a substance use disorder at 3-year follow-up (Iacono, 1998). Examining an adolescent sample, Hill and Steinhauer (1993) found decreased P3b amplitudes for at-risk prepubertal males, but a tendency toward *increased* amplitudes in postpubertal subjects. However, others have argued that once premorbid symptoms (e.g., history of conduct disorder) have been taken into account, effects of family history become insignificant (Bauer, 2001).

Amplitude effects have also been noted in adults with confirmed substance abuse disorders. Bauer (2001) reported decreased P3b amplitudes in opioid, cocaine, and cocaine-and-alcohol users, relative to controls; the three drug-use groups did not differ. He also reported significant correlations between these amplitudes and both duration of drug abstinence and number of reported childhood conduct disorder criteria. In a paradigm employing verbal (letter) stimuli, Kostandov and co-workers (1982) found decreased P3b amplitudes as well as increased latencies in recovering alcoholics, effects that appeared specific to the right hemisphere (RH). Similarly, Ciesielski and co-workers (1985) noted smaller P3b amplitudes on the right in alcoholics, while the opposite asymmetry was observed in controls. However, some studies found normal P3b amplitudes in addicted adults (e.g., Hill and Steinhauer, 1993; Hill et al., 1995; Lille et al., 1987). Some authors argued that this amplitude "normalization" may reflect developmental maturation effects ("maturing out") common to addictive behaviours (Hill et al., 1999; Bauer, 2001). If this is the case, it stands to reason that reduced amplitude, rather than predicting future tendencies, represent an index of current susceptibility. In support, Bauer (2001) reported a correlation between P3b amplitude and length of abstinence.

However, while the reduced amplitude of the P3b has been associated with vulnerability to substance abuse, reports of decreased P3b amplitudes are also common to other pathophysiological conditions (Hill et al., 1995), and so may represent a more general marker of psychiatric dysfunction (Iacono, 1998). For example, reduced amplitudes of this waveform have also been noted in depression (Roth et al., 1981), Parkinson's Disease (Wang et al, 2000), schizophrenia (Pfefferbaum et al., 1984), Attention Deficit Hyperactivity Disorder (Steger et al., 2000), and other deviant behavior in adolescents (Berman et al., 1993). Similarly, reduced P3b amplitude has also been hypothesized as reflecting a range of cognitive insufficiencies, including developmental delay, motivational deficits, and cortical disinhibition (Iacono, 1998). Blum and co-workers (1994) found no difference in P3b amplitude as a function of psychopathology; nor were there any clear effects of polysubstance abuse or dependence. Hence, reduced P3b amplitudes are limited in their explanatory power.

At the same time, generator sites for the P3b waveform do not appear to be related to hypothesized regions of damage resulting from substance abuse. Specifically, the P3b appears to be vulnerable to temporoparietal damage (Knight and Scabini, 1998), although other cortical and subcortical regions (Rodriguez Holguin et al., 1999), including the RH dorsolateral medial frontal gyrus (Kirino et al., 2000) have recently been implicated.

Similarly, while providing significant and compelling evidence that there are brain changes associated with addiction, the oddball task is generally not specific to deficits thought to underlie substance dependence. Use of the oddball paradigm is mainly due to convention, and the now-disputed contention (Johnson, 1993) that all P300 components arise from a single neural generator. As such, it lacks predictive power in assessing risk for dependence, as there is no *a priori* theoretical basis to expect substance dependent individuals to show decrements on the task. In general, most evidence suggests that the P3b elicited by the oddball task is only loosely related to the cognitive processes and brain regions of interest in dependence.

The P3a Waveform in Addiction

The P3a appears to be central to both the psychological processes and neurophysiological regions of interest in addiction, such as preferential attentional allocation to potentially salient events (Daffner et al., 2000) and involuntary orientation to novel, irrelevant, unexpected stimuli. Although the specific eliciting conditions are still under debate, studies attempting to dissociate the P3b and P3a components support the contention that they are distinct (Donchin et al., 1997). The P3a component (Squires et al., 1975), is distinguished from the P3b by its shorter latency, frontocentral distribution, and sensitivity to relatively "surprising" stimuli (Katayama and Polich, 1998). Katayama and Polich (1998) point out the role of the P3a in "frontocentral 'alerting'", directing the individual's attention to potentially salient events, particularly in a challenging task context. Verleger and co-workers (1994) made a similar distinction, arguing that the P3b actually indexes stimulus awaitedness, while it is the P3a that indexes *unexpectedness.* That is, the P3b is actually related to perceptual closure surrounding the completion of a subtask when an awaited event occurs, particularly when that event is rare (Kotchoubey et al., 1997). This contention is supported by studies finding shorter reaction times to standards that follow targets (i.e., following subtask completion) than those that follow irrelevant nontargets (Kirino et al., 2000). While the two components appear conceptually related, the P3a appears fundamental to processing "both stimulus and task novelty", particularly when those events involve feedback cues (Barceló et al., 2002).

Normal controls exhibit larger P3a responses lateralized over the RH in response to novel stimuli (Daffner et al., 2000). fMRI studies have confirmed the right PFC as a region of activation associated with the P3a, particularly in cases where subjects also showed a strong N400 response to novel identifiable stimuli (Opitz et al., 1999), which the authors suggested was associated with processing the sound's meaning. Given the link between the RH and P3a novelty responses, if the RH is differentially affected by addictive processes, the P3a response should be compromised.

Using a 3-stimulus oddball visual task (in which the third stimulus requires no response, but is "novel" or "unexpected"), Rodriguez Holguin and co-workers (1999) found P3a's to be more reduced in alcoholics than controls. Similarly, Hada and colleagues (2000) found decreased P3a's in response to alerting stimuli in an auditory version of this task. The authors also found differences between alcoholics and controls in current source density maps, which they interpreted as suggesting that alcoholics have disturbances in frontal regions interfering with P3a generation. Biggins and co-workers (1997) found reduced P3a amplitudes in cocaine abusers in both auditory and visual 3-stimulus oddball tasks. They also found delayed P3a latencies, which could not be explained by delayed latencies of earlier components. There was some correlation between both the amplitude and latency effects, and amount of either cocaine or alcohol usage, but not duration of abuse or length of abstinence.

However, not all ERP studies have suggested decreased P3a amplitudes in addiction. Polo and co-workers (2003) found a *larger* P3a over the left frontal region in alcoholics than in controls, and a polarity reversal of the subsequent reorienting negativity (RON). These authors interpreted their results as suggesting enhanced orienting of attention to novel, distracting stimuli among the alcoholic subjects. Ahveninen and colleagues (2000) found increased RT lags in alcoholics in response to deviant stimuli, as well as to the standards that followed them, indicating involuntary attentional shifting and impaired reorienting to the relevant task. These authors also found augmentation of the mismatch negativity (MMN) waveform, a component that reflects automatic detection of differences between auditory standard and deviant tones, but no difference in P3a amplitudes. Discrepancies in results between groups appear to reflect task differences, particularly in terms of the degree of attention required to perform the task. However, they could also reflect data manipulations such as subtraction that were used by some (e.g., Ahveninen et al., 2000; Polo et al., 2003), but not all, of the investigators.

Importantly, the P3a correlates specifically with prefrontal and subcortical damage (Knight and Scabini, 1998; Opitz et al., 1999), and appears to be related to activity in the NAcc (Zink et al., 2003). Patients with frontal lobe damage exhibit markedly reduced P3a amplitudes when viewing a novel stimulus, while P3b amplitudes remain intact, suggesting that "frontal lobe damage leads to diminished visual attention to novel events through its disruption of neural processes underlying the novelty [P3a] response" (Daffner et al., 2000). However, some imaging studies have failed to confirm this pattern of activation, finding RH medial frontal dorsolateral activation to target, but *not* novel, stimuli (Kirino et al., 2000). However, those authors noted that it may have been the lack of affective content in the novel stimuli that resulted in the lack of PFC activation, or that rapid habituation may have concealed the responses. Further, some activation in the RH inferior frontal gyrus, anterior to the insula, was noted. And because attenuation of the P3a is seen over both hemispheres following subcortical (hippocampal) damage, but only in the ipsilateral hemisphere following prefrontal cortical damage (Knight and Scabini, 1998), level of dysfunction may be discernable. Lateralization effects have also been noted, with asymmetric processing of novel stimuli by frontal lobe patients (Daffner et al., 2000). These studies suggest the P3a is more likely to be sensitive to damage in regions of the brain implicated in dependence, particularly lateralized neocortical damage, and so may represent a better index of damage in addiction than the P3b (Biggins et al., 1997).

The N200 Waveform in Addiction

A few studies have also found effects with the N200 waveform immediately preceding the P3a, either by itself, or as part of the N2-P3 cognitive complex. Like the P3a, the N2 waveform is thought to reflect automatic, preperceptual processing. It appears to be related to stimulus complexity and the physical properties of the stimulus, and is sensitive to subtle characteristics of cognitive tasks (Ciesielski et al., 1985). Realmuto and co-workers (1993) suggested that decreased amplitudes in the N2 and P3a waveforms may reflect a putative aberration in automatic processing, possibly in the generation of neural representations, or templates, necessary for matching infrequent deviant stimuli. In normal controls, the N2-P3 peak-to-peak amplitude has been shown to vary according to emotional content of the stimulus, with negative stimuli showing lateralization over the RH (Kayser et al., 1997). Again, available evidence suggests that the N2, like the P3a, may provide good discriminative capacity in addictive disorders, and be sensitive to relevant psychological processes.

To examine the role of automatic processing in alcoholics, Realmuto and colleagues (1993) used a modified oddball paradigm (in which subjects did not have to attend to the task), and found decreased N2-P3a peak-to-peak amplitudes in alcoholics, with the largest differences evident at frontal sites. Similarly, Ciesielski and co-workers (1985) reported abnormal lateralization in an N2-P2 peak-to-peak measure, although it is not clear from the nature of their analysis whether this effect was significant. Additionally, Hill and colleagues (1995) reported that N250 amplitude discriminates between users and nonusers.

Early Waveform Components in Addiction

Relatively few studies have examined the role of early, so-called exogenous waveform components in addiction. This is because characteristics of these components are primarily thought to be determined by the physical properties of the stimulus (Fabiani et al., 2000). Their relative lack of study in addiction may reflect the fact that "attention-related modulations of these early sensory evoked peaks are postulated to reflect the filtering or 'gating' of visual information *at or before the level of the visual cortex*" (Mangun & Hillyard, 1988; italics added). There is no *a priori* reason to expect perceptual processes to differ between addicts and normal controls.

However, attentional allocation also appears to play a role in these waveforms, as N1 and P2 components are enhanced during attentional allocation (e.g., counting tones, or attempting to "tune out" irrelevant stimuli). This has been described in both auditory (Hassett, 1978) and visual (Mangun & Hillyard, 1988) conditions. These findings make the potential relevance of these components somewhat more promising, although still dubious.

Overall, the available electrophysiology evidence suggests that the N200 and P3a may represent particularly good markers for substance dependence. Hence, it is hypothesized that craving severity will show an inverse relationship with amplitude of the P3a, N200, and N2-P3 peak-to-peak complex.

Task Specifications

Given the role of the PFC in complex, ambiguous, or unpredictable behaviour (Fuster, 2001), the chosen task was a modification of the "gambling task" (Bechara et al., 1996; alternately referred to as Bechara's gambling task, or the Iowa gambling task), a reinforcement-based learning game. In the original task, skin conductance responses were recorded as subjects chose a card from one of four decks at random. Each card had a point value ('positive' or 'positive + negative'; a breakdown of the rewards and penalty contingencies is described in detail in Bechara et al., 2001.), with the object of the task to gain as many points as possible.

Unbeknownst to the subject, two of the decks were accompanied by moderate wins and concomitant moderate losses. Reinforcement on the other two decks consisted of large wins, but the occasional very large loss, which would eradicate all previous winnings on that deck. Therefore, every card choice involved a judgement of relative risk (Grant et al., 2000). Hence, overall, it was a better strategy to bet on the first two decks, and a "high-risk" strategy to bet on the last two.

It was demonstrated that normal controls would learn to stay away from the high-risk decks (the advantageous strategy), while individuals with mediofrontal damage would not, instead relying on what Paulus et al. (2002) refer to as "stimulus-contingent response selection". In fact, "ventromedial prefrontal patients… select more from the disadvantageous decks than from the advantageous ones… [they] appear insensitive to the future consequences of their actions, and are thus guided by immediate prospects" (Bechara et al., 1996). However, there are several feasible explanations for poor performance on this task, including a preference for high-risk options, a hypersensitivity to potential reward, an insensitivity to punishment, difficulty in computing risk probability, or more general impairments in learning reward and punishment associations (Clark et al., 2003).

Recent research has suggested that this task may be particularly sensitive to damage in the RH. Two studies (Clark et al., 2003; Tranel et al., 2002) of matched right- and left-lesioned subjects found that individuals with RH lesions selected more cards from the "risky" decks; moreover, task scores correlated with total lesion volumes in the medial prefrontal, middle, and superior frontal gyri (notably, outside the ventromedial regions). Conversely, LH lesioned patients generally performed like normal controls, with no correlation between score and lesion extent. Again, sensitivity to RH damage suggests that the gambling task may be particularly suited to an addicted population.

Because the inability to abstain from drug or alcohol use despite negative consequences is a hallmark of dependence, the gambling task has strong face validity for examining the cognitive deficits underlying addiction (Grant et al., 2000). Recently, research confirmed that almost two-thirds of substance dependent patients performed within the range of patients with ventromedial damage, while only a third of controls fell within that range (61.0% vs. 32.5%; Bechara et al., 2001). Differences could not be explained by demographic variables (age, sex, education), nor did it correlate with traditional measures of frontal lobe function (Bechara et al., 2001). The authors suggested that decision-making impairments in substance dependence may reflect ventromedial damage, at least in a some individuals. Additionally, polysubstance abusers perform more poorly on the gambling task than do controls (Grant et al., 2000), as do heroin addicts (Petry et al., 1998) and individuals with antisocial personality disorder (Mazas et al., 2000), a known vulnerability marker for alcoholism. Furthermore, magnitude of the performance deficit correlates with average quantity of alcohol consumed, although not with frequency of consumption (Mazas et al., 2000). However, research with cocaine addicts failed to confirm a performance decrement (Adinoff et al., 2003). Further, these studies did not directly examine factors such as how level of withdrawal influences task performance or related structural activity.

A second important finding from the Bechara et al. (1996) study was that when normal controls picked from the high-risk decks, they would exhibit anticipatory skin-conductance responses (SCRs; Bechara et al., 1996), an index of autonomic activity related to preparatory behaviour (Gruzelier et al., 1988) presumably indexing risk-taking. Again, these results may be suggestive of RH damage, as SCRs appear particularly sensitive to damage in this region (Tranel and Damasio, 1994). Tranel and colleagues (2002) found that anticipatory SCR amplitudes in a RH-damaged group were similar to individuals with bilateral damage, and significantly lower than a group with comparable LH damage. A review of previous SCR studies notes that they also predominantly implicate prefrontal cortical regions (Papousek and Schulter, 2001).

Similarly, an ERP of ADHD children showed a right prefrontal deficit (Pliszka et al., 2000), supporting the notion that damage to the RH may be associated with the inability to develop anticipatory warning or inhibitory cues. Specifically, the experimental group failed to generate the normal slow positive preparatory wave preceding the Stop signal in failed inhibition trials. While the neural structures underlying ERPs and electrodermal measures are not identical, high correlations in the activity of the two systems have been noted, leading some authors to speculate that they are "structurally linked" (Lim et al., 1996). In support, correlations between the amplitude of the P3a and SCRs have been reported (Knight and Scabini, 1998).

In general, imaging studies point to altered activity in the PFC, often of a lateralized nature. fMRI activation in the left ventromedial region has been noted among adolescents with alcohol use disorders (Tapert et al., 2003). Another fMRI study by Paulus and co-workers (2002) using a decision-making task found activation in the left middle frontal gyrus and bilateral ventromedial PFC in controls during prediction of the subsequent trial, while methamphetamine addicts lacked this activation. Moreover, lack of ventromedial activation, particularly in the RH, was related to duration of abuse. In addition, the experimental group tended to switch strategies inappropriately, a performance decrement that normalized with length of sobriety. Similarly, go/no-go tasks, which examine response inhibition, show a correlation between false alarm rate and activation in orbitofrontal and anterior cingulate regions (Casey et al., 1997) Using a different feedback task, Martin-Soelch and co-workers (2001) found bilateral activation in regions including the orbitofrontal and dorsolateral cortex in healthy controls, whereas smokers showed activation only in the left orbitofrontal region, left midbrain, and right cingulate gyrus. A study of the effects of feedback on planning in normal controls found decreased activity in the right anterior frontal and inferior frontal gyri, with concomitant increases in activation of the right thalamus and insula (Elliott et al., 1997). Finally, a study employing the gambling task found that cingulate and LH dorsolateral (but not orbitofrontal) rCBF activation correlated with performance on the task, although this was irrespective of drug use history (Adinoff et al., 2003). Hence, the PFC regions appear sensitive to manipulations of feedback and behavioural inhibition.

These lines of evidence led us to believe an ERP-modified version of the gambling task would have predictive power in alcoholics and cocaine addicts, given their proposed cognitive deficits and hypothesized asymmetric prefrontal damage. Notably, the task bears conceptual similarity (in terms of presentation of cues predicting reward or punishment) to that of Sobotka and colleagues (1992), which found lateralized approach and withdrawal mechanisms associated with computerized wins and losses, correlated with EEG asymmetries. Modifications made to the task capitalized on the fact that the model we are testing proposes coordinated alterations in hemispheric functioning. Since the LH is important for "linear" processing of sequentially presenting familiar stimuli (e.g., verbal statements, mathematical propositions, rapid motor sequences) whereas the RH is superior for "configurational" processing and best suited to handling novel information and, presumably, affective information (Lezak, 1995), we used a string of novel, emotionally-loaded stimuli (cues and reinforcers). Also, because the RH is thought to be superior in the processing of global information, while the LH is more detail-oriented, we utilized a task in which responses to each stimulus are influenced by the overall probability of winning for that stimulus.

We hypothesized that, if correlations exist between one's level of dependence (as indexed by cravings), and lateralized damage in the PFC, then cravings should correlate with scores on the task as well as with concomitant electrophysiological indices of brain functioning. Hence, one objective of our research was to determine whether there was any correlation between cravings and amplitude of the P3a and N200 waveforms. A parallel objective was to determine whether there was any correlation between craving and task performance.

Materials and Methods

In order to collect ERP data, certain modifications to Bechara et al.'s (1996) task were necessary. Because ERPs are sensitive to eye movement artefact, stimuli were presented one at a time on the centre of a computer screen. In order to present the four "decks", coloured shapes were presented signalling the opportunity to "place a bet", in order to try to win points. However, in the original task the positive and negative values were presented simultaneously on the same card, whereas in this task only the adjusted score was presented (e.g., +75/-25 was presented as +50). As in the original task, two of the stimuli were followed by larger payoffs and occasional very large losses (i.e., were "high-risk"), while another two had smaller wins but smaller concomitant losses. In addition, a fifth stimulus with equal probability of wins/losses (i.e., mean 0) was included as a control. As in the original study, subjects were not told the probabilities related to each stimulus *a priori,* as the objective was to learn these contingencies over the course of the task.

In our task, the individual was instructed that he would be playing a game, consisting of placing bets (by clicking a mouse button) on a number of shapes. He was informed that after each shape he would find out how much he had/could have won or lost (the contingent point value would be presented whether or not the indvidual placed a bet). The subject was not compelled to press the button to any particular shape, but was simply told to try to "get as many points as possible, or avoid losing points as much as possible". A graphic illustration of the procedure is presented in Figure 5.1.

Since the generation of ERPs depends on the averaged response to many trials, the number of stimuli in the revised task was increased from 160 to 800 (160 per category, including the control). However, the stimuli in our task were matched to the original in terms of means (-25 for the high-risk stimuli, and +25 for the other two) and approximate standard deviations (see Table 5.1, and Figure 5.2 for a side by side comparison of histograms comparing the two tasks).

Another discrepancy between the two experimental designs was the presentation rate of the stimuli. In order to elicit impulsive responding, stimuli were presented at a rapid rate (every 1.4 s), rather than having individuals choose from decks *ad libitum.*

A final discrepancy between the tasks was the presentation of stimuli in consecutive blocks. Between blocks, individuals were asked how much they believed they had won or lost. As Grant and co-workers (2000) note, "drug abusers may continue to choose cards from the low yield decks in the Gambling Task because they underestimate the magnitude of their losses occurring over an extended period" (Grant et al., 2000). Hence, this task modification directly compared the individual's assessment of his performance with his actual score.

This experimental design also allowed us to make two very specific hypotheses regarding expectation and emotion. First, if the neural processes underlying expectation differ as a function of craving, then ERP responses to the cues (stimuli signaling an opportunity to place a bet based on a prediction of the odds of winning) should differ depending on type of stimulus (i.e., safe *vs.* risky). It was hypothesized, in view of the results of previous studies, that craving severity would be associated with reductions in the P3a and N200 to the risky stimuli. Further, we hypothesized that cue responses should be lateralized to the LH.

Second, if the neural processes underlying emotion differ between groups, ERP responses to the reinforcers (actual wins and losses) should differ as a function of craving severity. Because the reinforcers are thought to index RH affective processes, we hypothesized that severity would directly correlate with increased amplitudes of the P3a, reflecting hyperreactivity to reward/punishment, and that these responses would be lateralized to the right for penalties and to the left for rewards.

Power Calculation

Our next step was to determine the minimum number of subjects required to achieve significant results, given actual differences between the groups. It was decided *a priori* that individuals would be grouped according to low, medium, or high craving, as based on MMCQ scores (described in detail in Chapter 5). It was determined that half these subjects would come from an alcohol craving population, while the other half would come from a cocaine craving population.

In order to determine the exact number of individuals required, the power calculation given in equation 1 (Kirk, 1995) was used:

$$\phi = \sqrt{(\Sigma\alpha^2/p) / (\sigma^2/n)} \qquad (1)$$

This formula determines the value of the value of ϕ, the minimum acceptable value for the desired power in order to detect an effect, (in our case 80%, a value conventionally considered a good balance between Type I and Type II error); a value of 1.9 α represents the desired effect size (in our case, ½ a SD), σ^2 represents the population variance. These corresponded to values of 1.26 and 6.39 respectively, as calculated from previous ERP data gathered in our lab using the same equipment. Finally, *p* represents the number of groups (i.e., the three craving groups - low, medium, and high - as decided *a priori*), such that *n* gives the required sample size per cell.

Based on this calculation, it was determined that the experiment would require 14 individuals per group, for a total *n* of 42. Further, half of these individuals would comprise the alcohol subgroup, and the other half would comprise the cocaine subgroup.

From the original sample of 51 subjects included in the neuropsychological and questionnaire analyses, electrophysiological data from two individuals was lost due to computer error. One subject refused to continue following the first half of electrophysiological recording, and his data was excluded; one other subject refused after 7 (of 8) blocks, but had enough EEG data to meet criteria for inclusion. Of the remaining subjects, exclusion was limited to excessive EEG artefact, which eliminated another 6 subjects, for a final total *n* of 42.

Electrophysiological Recordings

Subjects were seated in a dimly lit, sound-attenuated chamber, one meter from the computer monitor. They were asked to sit in a relaxed position with their dominant hand on a computer mouse on the table in front of them. They were asked to blink and move around as little as possible, in order to reduce potential EEG artefact. Finally, they were instructed to respond as quickly as possible by pressing the mouse button once they had made the decision to place a bet.

Continuous EEG signals were recorded using a 128-channel dense sensor array (Geodesic Sensor Net; Electrical Geodesics, Inc.). This net does not employ the traditional 10-20 system (Jasper, 1958); rather, Ag/AgCl electrodes are placed in an icosohedron configuration, approximately equidistant from one another. However, most electrodes from the 10-20 system bear a rough correspondence to some electrode in the 128-channel configuration (Figure 5.3).

Net application required 10-15 minutes on average. Net placement is determined via positioning of certain reference electrodes over known anatomical markers, namely the mastoids, vertex, and forehead ground. Contact is established via carbon fiber electrodes fitted with electrolytic sponges embedded in the net; each electrode is adjusted to a perpendicular position over the scalp, and gently rubbed to improve contact. Individual electrode impedances were kept below 60 kOhm; while this level is higher than traditionally accepted, it does not pose a problem for EEG recordings using a high input impedance amplifier (200 MOhms; Ferree et al., 2001). To facilitate the application process, prior to cap placement a saline solution was lightly applied to each subject's head using a damp facecloth. Additional solution added at individual electrode sites when impedances exceeded allowable levels (> 60 kOhms). For more information on cap specifications and application, the reader is directed to http://www.egi.com/gsn.html.

EEG amplification was accomplished using the Net Amps 200 system (Electrical Geodesics, Inc.), with built-in 16-bit A/D conversion and integrated simultaneous sample and hold. All readings were taken using a band pass from 0.1 Hz to 30 Hz, in reference to the vertex electrode, which was later converted to a common average reference. Electro-occulogram (EOG) eye-movement artefact exceeding 70μV was measured via activity recorded at the infra-orbital and outer canthus regions of each eye, and affected segments were automatically excluded. Digital Absolute Level Detection routines built into the NetStation 3.0 package were used to remove any traces with amplitudes exceeding 95% of the peak A/D range.

The modified task, as described above, was presented to the subject. Essentially, subjects were told that they were going to play a game, the object of which was to gain (or avoid losing) as many points as possible. They were told they would be presented with a continuous series of 5 shapes, on which they could "bet". After each shape, they would would see a point value indicating how many points they had won/lost (or would have won/lost, if no bet was placed) for that trial. The following example was read for clarification, and reiterated as necessary:

> "Let's say you see a square, and you hit the button, then you see a 50. That means you won 50 points. If you see a circle, and you hit the button, and then you see a *minus* 100, that means you *lost* 100 points. Then let's suppose you see a triangle, and you *don't* hit the button, and then you see 200. That means you *could* have won 200 points, but you didn't win anything at all, because you didn't hit the button; you didn't place a bet. Do you understand?"

Subjects were told that some shapes were "worse than others", but that they could win by "stay[ing] away from the worst shapes". Finally, they were told they must play until the computer stops, and that they would be given breaks, at which point they were to estimate their task performance during that block. It was emphasized that it was more important to play the game to the best of their abilities, and that it was alright to guess if unsure. They were also told that the experimenter did not know the true score, and could not verify how they were "really" doing. Specific task instructions are presented in full in Appendix B.

Stimuli were presented every 1400ms; each trial consisted of a 200ms prestimulus period of which the last 100ms comprised the prestimulus baseline, followed by a 100ms presentation of the stimulus, with 900ms of EEG recorded post-stimulus, and an intertrial interval (ITI) of 200ms (presented diagrammatically in Figure 5.4). Continuous data was sampled at a rate of 250 samples/second. The subject's key presses and associated reaction times, as well as information regarding the nature of the trial type (e.g., cue type, or reinforcement value) were automatically encoded along with the associated EEG activity.

Data Reduction and Analysis

Both performance measures (button presses in response to the task; estimates of performance), and electroencephalographic data were analyzed. For the performance measures, analyses were carried out on the full group of 51 eligible subjects, as exclusion criteria for ERP collection (e.g., excessive eyeblinks or movement; EEG recording problems), did not preclude acceptable behavioural data on the part of the subject.

Statistical techniques used to examine these measures are discussed below. All statistical analyses were performed using the *Statistical Package for the Social Sciences* (SPSS) student version 10.0.5.

Performance Measures

Three measures of task performance were computed, to examine systematic differences in cognition or behaviour as a function of craving severity. The first evaluated actual performance relative to estimated performance. The second measure examined behavioural change over the course of the experiment. The third examined advantageousness of responding over the course of the task, and was included *post hoc* since it has been utilized in recent studies employing this task (e.g., Grant et al., 2000; Mazas et al., 2000).

Actual and Estimated Task Performance. It was predicted that craving severity would be associated with poorer task performance. In addition, it was predicted that craving severity would correlate with overestimates in task performance (i.e., they would perceive their performance as better than it actually was), due to the hypothesized deficit in the ability to evaluate reinforcement feedback.

Both actual and estimated scores were log transformed prior to analysis, in order to normalize their data distributions. This is important because data normality is one assumption of parametric statistical analysis. Log transformation takes account of the relationship between the size of the residuals and the size of the dependent variable by applying stronger correction for larger values (for a detailed discussion, the reader is referred to Hopkins, n.d.). A constant was added to all values preceding transformation, as negative numbers cannot be log transformed. Then, repeated measures analyses of variance (ANOVAs) were run on both sets of scores.

Changes in Cue Response Behaviour. A direct relationship between craving and responding was anticipated, with the high craving group showing the highest rates of responding, due to their hypothesized deficit in learning the task. Role of affective valence was examined, with no *a priori* hypotheses regarding the nature of the relationship between craving and responding to affective cues.

Actual button presses were generally normally distributed, so these variables were not transformed. In order to examine learning over the course of the task, a regression line of the actual points won/lost was calculated for each cue type, for each individual. Over the 8 blocks of trials, subjects were expected to learn that two of the cues were generally associated with more penalties than rewards, another two of the cues were associated with more rewards than penalties, and that one cue had an equal number of rewards and penalties. It was also hypothesized that slopes of button pressing over the course of the blocks would reflect this assertion: Presses would decrease to the first set of cues ($slope<0$), increase to the second set ($slope>0$), and remain stable for the neutral cue ($slope=0$).

Independent t-tests were used to compare slopes between the alcohol and cocaine groups, while one-way ANOVAs were used to compare slopes in the low, medium, and high craving groups.

Advantageousness of Responding. A coefficient was computed by subtracting the number of button presses to disadvantageous ('bad') cues from the number of button presses to advantageous ('good') cues to obtain a measure of overall advantageous responding (i.e., good -

bad). Additionally, in order to control for potential differences in the rates of responding, a rate measure comprised of number of button presses to advantageous cues as a proportion of total button presses (good/total) was computed. This measure was calculated separately for each block, and then an average was obtained, as initial observations suggested that rates of responding may not remain stable over the course of the task.

Pearson correlations between these measures and measures of drug-taking were utilized.

Performance Results

Actual and Estimated Task Performance. No significant differences were noted between the actual scores of the two groups.

Similarly, no differences were noted between estimated scores of the groups, although differences approached significance ($F = 2.48, p < .10$), indicating a tendency for decreased performance estimates in the high craving group and increased estimates in the low craving group (Figure 5.5). That is, there was a systematic relationship between craving and estimates of one's performance, such that stronger cravings were associated with a tendency to perceive one's performance as worse than were weaker cravings. While the effect was not significant, insomuch as the cocaine and alcohol groups can be considered independent replications the fact that this trend was evident in both somewhat increases our confidence in this finding.

Changes in Cue Response Behaviour. Craving was significantly correlated ($r = .286, p < 0.05$; see Figure 5.6) with increased responding, but only during the first block of trials (all successive blocks, p's > .3). Furthermore, elimination of one obvious outlier (in the upper-left quadrant of the scatterplot) increased the correlation substantially ($r = .385, p < 0.01$).

There were no differences in response slopes between the alcohol and cocaine groups (all p's > .75). Similarly, ANOVAs failed to reveal differences between the craving groups for the response slopes. Moreover, response slopes to the risky stimulus were opposite our hypotheses, as the *low* craving group actually demonstrated the largest slope increment in response to this cue (see Figure 5.7), suggesting they had the most difficulty learning the risky response contingency. Visual inspection, however, revealed a different pattern of response slopes between the groups (Figure 5.8, collapsed to illustrate patterns of responding to negative, positive, and neutral cues). Hence, a MANOVA was performed to examine the response slopes to the five different cue types between the craving groups. The MANOVA resulted in a significant F-value$_{(5,37)}$ of 2.54 ($p <$ 0.05, Roy's Greatest Characteristic Root Test). However, neither of the resulting discriminant analysis functions reached significance.

Advantageousness of Responding. While the group of Mazas and co-workers (2000) found a correlation between disadvantageousness of responding and weekly quantity of alcohol consumed in a sample of alcoholics and antisocial personality disorder individuals, our study found no correlation ($r = .032, p > .8$).

Interestingly, however, when examining cocaine addicts[15], a strong correlation was found between disadvantageous decision-making and frequency of use ($r = -.440, p < .05$); this relationship remained even after removing anyone with the maximum daily frequency, to eliminate possible ceiling effects ($r = -.576, p < .05$). Further, it was strengthened after controlling for the effects of differences in rate of responding ($r = -.602, p < .05$). A scatterplot depicting this relationship is presented in Figure 5.9. Again, for the cocaine group, no relationship was found with quantity ($r = -.135, p > .6$).

Electrophysiological Measures

Because most of the ERP literature reviewed concerning addiction (Ahveninen et al., 2000; Blum et al., 1994; Hada et al., 2000; Hill and Steinhauer, 1993; Iacono, 1998; Polo et al., 2003; Realmuto et al., 1993; Rodriguez Holguin et al., 1999; although see Kostandov et al., 1982), or related variables, such as anxiety (Grillon and Ameli, 1994), emotional processing (Cacioppo et al., 1996; Laurian et al., 1991), or presence of the A1+ genotype (Ratsma et al., 2001; although see Blum et al., 1994) failed to demonstrate any effect of latency, and because latency has not been shown to produce good long-term test-retest reliability (Sinha et al., 1992) and is not believed to have a significant genetic component (Hill et al., 1999), latency measures were not analysed[16]. Hence, only amplitude data will be discussed herein. Amplitude peak windows (the range within which the peak amplitude must fall) were chosen by visual inspection of the grand average, checking back to individual files to ensure no peak was outside the latency parameters.

Segmentation, a process that involves choosing the acceptable trials to be included in each average waveform, breaks data into within-subjects factors. This process involves several derivation operations, outlined here.

Immediately prior to segmentation, the data is lowpass filtered to remove frequencies not of interest (in our case, frequencies above 12 Hz). Once the segments have been defined, the software applies an algorithm to remove any eyeblinks or movement artefact. At the same time, any bad channels (e.g., electrodes with poor contact) are removed from analysis. These are then replaced with data interpolated from remaining surrounding channels, based on the assumption that channels in close proximity have similar data due to volume conduction. Averaging is then performed, at which time the data is rereferenced to the average reference. In order to control for the fact that the surface of the head is unevenly sampled, a polar average reference is applied. Finally, the data is baseline corrected to determine a new zero-voltage value. For a greater discussion of any of these operations, the reader is referred to the Net Station Viewer and Waveform Tools Tutorial (contact info@egi.com for more information on obtaining a copy of this document).

Data was automatically segmented using the Net Station 3.0 software routine off-line. Within-subjects factors of stimulus type (cues 1-5; reinforcers good, bad, and neutral), and electrode group (of 7 total) were utilized. To be included in the analysis, an individual required a minimum of 8 artefact-free trials per category, with an average of at least 20 trials across categories.

In terms of reducing the 128 electrodes into topographical regions for analysis, preliminary examination of 20 subjects revealed that PCA was not appropriate (i.e., did not yield comparable patterns of factor loadings between subjects). Hence, subsets of electrodes were selected to represent frontal, central, parietal, and lateralized responses *a priori*. 7 subsets were delineated, with approximately equal numbers of electrodes in each group (shown in Figure 5.10).

Repeated measures analyses of variance (ANOVA) with either craving group (three levels) or drug group (alcohol vs. cocaine) as between-subjects measures were used to compare the electrophysiological variables. Homogeneity of variance between groups was assessed via the Mauchly sphericity test. When the data significantly violated this requirement for repeated measures, a Greenhouse-Geisser adjustment of the degrees of freedom was made to calculate a more conservative *p*-value for each *F* ratio. Uncorrected degrees of freedom are reported, along with corrected *p*-values. Where *F* values involving craving group were significant, *post hoc* comparisons were made using the Tukey procedure.

To explore the lateral distribution of P3 measures from the two electrode groups over each hemisphere, followup analyses were then conducted yielding separate amplitude scores for the LH and RH. Similarly, in this analysis, cues were reduced by valence to good, bad, and neutral. To reduce the likelihood of Type I errors in the follow up analyses, effects were evaluated only if higher order interactions including site were observed or if effects were explicitly hypothesized i.e., main effects of valence, laterality, and their interaction.

Data for the four component measures (N170, P200, N170-P220 peak-to-peak measurement, and the P3b) were analyzed separately for each group, where applicable. Amplitude effects were examined separately for cue and reinforcer stimuli. In addition, a comparison was first made of the groups in terms of their artefact free EEG trials. These measures are described below.

Artefact-Free Trials. Prior to examination of the EEG, a preliminary analysis was performed to check whether there were differences in the number of acceptable (artefact-free) EEG trials, as a function of craving group, drug group, stimulus type (cue *vs.* reinforcer), or stimulus valence.

Cue Analysis. Cue analysis examined responses to the 5 different cue types, (i.e., the four in the original Bechara gambling task, plus the neutral cue), each presented a total of 160 times throughout the task. Segments consisted of all artefact-free trials for each cue type.

While other analyses of the cue data are theoretically possible (e.g., changes in responses to cues over blocks), their composite *n*'s were necessarily smaller due to lower numbers of acceptable trials, and so further analyses breaking down cue responses were not conducted.

Peaks of the N170 and P220 were determined by taking the point of lowest (N170) and highest (P220) frontal baseline-to-peak amplitude within the latency window of 132-288 ms. Peak-to-peak amplitude of the N170-P220 was obtained by measuring the distance along the voltage axis between the two peaks (cf. Ciesielski et al., 1985). Amplitude of the P3b was obtained using the traditional baseline-to-peak measurement, by taking the point of highest peak amplitude over the parietal cortex within the latency window of 288 - 600 ms.

Reinforcer Analysis. Because reinforcers were less frequent (i.e.. the risky stimulus was, by its nature, rare and unpredictable; the "-1150" score occurred only 16 times throughout the course of the task), they were blocked by valence. Subsets of approximately equal numbers of reinforcers from the three valence categories (negative $n = 80$; positive $n = 80$; neutral n = 76) were chosen for analysis. Overall, there were 80 negative (mean -390, SD 383.72), 80 positive (mean +100, SD 0.00), and 76 neutral (mean 0, SD 0.00) reinforcers.

Latency ranges for the reinforcers generally approximated those of the cues. However, as will be discussed in the following section, reinforcers did not elicit an early negative component.

Hence, for the P220 measure alone, the peak latency window was from 120-288 ms, while the P3b peak latency window spanned the range of 288-652 ms.

Results

Artefact Free Trials. The mean (SD) number of acceptable trials (per person) for the cues was 107.21 (30.93). For the reinforcers, the corresponding value was 44.17 (18.31). The divergence of these values reflects the fact that there were more cues (160 per category) than reinforcers (*n*'s between 76-80). Expressed as a proportion of total possible trials, this equates to 67.0% (19.33) of the cues and 56.2% (23.28) of the reinforcers were artefact-free, a statistically significant difference favouring the cues ($t = 4.821, p < .001$).

Proportion scores were used to compute a repeated measures ANOVA comparing the probability of acceptable responses for the groups (no comparisons required Greenhouse-Geisser correction). There was no main effect of craving severity ($F_{2,38} = .43, p > .6$), nor drug type ($F_{1,38} = 0.97, p > .3$), nor was there any interaction of the two ($F_{2,38} = .12, p > .8$).

In terms of within-subjects effects, there was a significant effect of stimulus type (cue *vs.* reinforcer, $F_{1,38} = 21.57, p < .001$), but no interaction of stimulus type with either drug or craving group. In addition, there was a main effect of valence, ($F_{2,76} = 11.24, p <.001$); again, there were no significant interactions with drug or craving group, although the latter approached significance ($p < .07$). The valence effect reflected the fact that negative stimuli generally produced the lowest number of acceptable trials, while neutral stimuli produced the highest number. However, there was also a significant stimulus x valence x craving interaction ($F_{4,76} = 3.64, p < .01$), demonstrating variations among this general pattern as a function of craving. For the cue stimuli, positive stimuli produced more acceptable trials for all three craving groups. However, separate paired t-tests within each craving group, using Bonferroni correction for multiple comparisons, did not verify that this difference was statistically significant. For the reinforcer stimuli, positive stimuli produced the most acceptable trials for the low craving group, but neutral stimuli produced more for the medium and high craving groups. Again, paired t-tests were performed to examine the pattern of results. These confirmed that, in the low craving group, positive stimuli produced significantly more acceptable trials than negative stimuli (58.4% *vs.* 51.3%; $t = 02.71$, $p < .016$); no other comparisons were significant. For the medium craving group, rates of acceptable trials were higher for neutral than negative trials (59.2% *vs.* 49.3%; $t = -3.74$, $p < .01$), as was also the case for the high craving group (67.9% *vs.* 53.9%; $t = -4.73$, $p < .001$); other comparisons were not significant at the .0167 level. These results are presented for the cues and reinforcers in Figures 5.11a and 5.11b, respectively.

This pattern of results suggests that craving may play a role in cognitive processing of cue *vs.* reinforcer stimuli, and that this effect could be valence-dependent.

Cue Responses. Cue response waveforms for the 5 cue types are presented in Figures 5.12 - 5.16. Accompanying brainmaps illustrating the surface brain potentials in the range of the N170-P220 (Figures 5.17 - 5.19) and the P3b (Figures 5.20 - 5.22) response range for each group follow. An overview of the results is presented in Table 5.2. Findings are described in detail below, however in the interest of both brevity and clarity, discussion of significant interactions is confined to interactions involving craving.

For the *N170* and the *P220*, there were no significant effects involving craving. However, effects for both of these measures tended to approach significance, and displayed similar patterns of results. As a result, we chose to examine whether the *N170-P220 peak-to-peak* measurement, which spans the full range of interest, would yield significant differences.

The 5 by 7 repeated-measures ANOVA revealed a significant effect of craving group ($F_{2,42} = 3.87$, $p < .05$), with Tukey *post hocs* showing a significant difference between the medium and high craving groups ($p = .045$). This pattern of results reflected the fact that there was a lower overall peak-to-peak range for the high craving group than the other groups. In addition, there were significant main effects of stimulus ($F_{4,168}$ = 10.73, GG = .711, $p < .001$), electrode group ($F_{6,252}$ = 28.50, GG epsilon = .635, $p < .001$), and a significant stimulus by electrode group interaction ($F_{24,1008}$ = 4.33, GG epsilon = .433, $p < .001$). As illustrated in the brainmap figures (5.17 - 5.19), the greatest positivities were generally observed in response to the high-risk stimulus (column 2) while the greatest negativities were seen to the most consistently rewarded stimulus (column 3), primarily in the frontal regions. Lateralization differences in this pattern between the groups were reflected in a two-way interaction of stimulus and craving which approached, but did not meet, significance ($F_{8,168}$ = 2.02, GG = .711, $p < .10$).

In order to further examine whether there were any effects of lateralization or valence, data of the two electrode groups over the LH and RH were collapsed to yield scores for side, while the cue types were collapsed into positive, neutral, and negative valence. Hence, a 2 (side) by 3 (valence) repeated-measures ANOVA was performed. After having collapsed scores, the main effect of craving remained significant ($F_{2,42}$ = 3.22, $p < .05$), as did the main effects of side ($F_{1,42}$ = 14.96, $p < .001$) and valence ($F_{2,84}$ = 25.53, GG epsilon = .861, $p < .001$). There were no significant two-way interactions with these variables. However, there was a marginal three-way interaction of side x valence x craving ($F_{4,84}$ = 2.34, GG epsilon = .834, $p < .10$), reflecting a relationship between hemisphere and valence which differed systematically between the groups. Paired t-tests were used to explore whether there were hemispheric differences as a function of affective valence that differed between the craving groups. For all craving groups, amplitude ranges to affective cues were greater over the RH. However, for the low craving group, this difference was only significant for the positive cues, which showed a pronounced negativity over the LH which was absent over the RH (t = 2.72; $p < .05$). No significant differences (at the Bonferroni-corrected level of .0167) were found for the medium craving group. For the high craving group, only responses to the high-risk stimuli showed significant lateralization, with stronger positivities over the RH. Hence, overall, lateralization was greatest for positive cues in the low craving group, and for high-risk (negative) cues in the high craving group. A line graph displaying these interactions is presented in Figures 5.23a-c for the low, medium, and high craving groups, respectively.

For the *P3b*, the 5 by 7 repeated-measures ANOVA revealed only a significant effect of electrode group ($F_{6,252} = 28.03$, GG epsilon = .403, $p < .001$), reflecting the conventional focus of the P3b over the parietal cortex. There were no interactions involving craving.

When scores were collapsed, a significantly main effect of side emerged ($F_{1,42} = 24.31$, $p < .001$) demonstrating that P3b amplitude was shifted somewhat over the RH. No other significant main effects or interactions were observed.

Reinforcer Stimuli. As with the cues, reinforcer response waveforms are presented in Figures 5.24 - 5.26 for the negative, neutral, and positive stimuli, respectively. Accompanying brainmaps are presented for the N170-P220 and the P3b ranges in Figures 5.27 - 5.29 and 5.30 - 5.32, respectively. Results are presented in Table 5.3.

As noted above (and as illustrated in Figures 5.24 - 5.26), the reinforcers, unlike the cues, did not elicit an N170 waveform component, *per se*. In general, the negative deflection did not cross baseline over the frontal or central regions. Therefore, analyses are limited to the P220 and P3b components.

For the *P220*, the 3 x 7 repeated-measures ANOVA revealed no effect of craving, but significant main effects of stimulus ($F_{2,84} = 20.56$ $p < .001$), electrode group ($F_{6,252} = 29.16$, GG epsilon = .317, $p < .001$), and a significant stimulus by electrode group interaction ($F_{12,504} = 7.16$, GG epsilon = .481, $p < .001$). These reflected the fact that responses to neutral stimuli (i.e., scores of "0") produced much lower amplitudes than either wins or losses, as can be observed in brainmap Figures 5.27 - 5.29. The interaction of stimulus x electrode group revealed that the effects to the valenced stimuli were generally shifted over the LH in comparison to the neutral stimuli. Again, no interactions involving craving were observed.

When scores were collapsed to examine possible effects of lateralization, the effects of craving group approached, but did not meet, the .05 criteria, of significance ($F_{2,42} = 2.79, p < .10$), with Tukey *post hocs* revealing the largest difference between the low and high craving groups. There was a significant main effect of valence ($F_{2,84} = 24.42, p < .001$), with paired t-tests confirming significant differences between all valence categories (negative > positive > neutral; *t*'s for all comparisons > 3.6; all *p*'s < .001). That is, P220 amplitudes were largest for losses, intermediate for gains, and smallest for '0' scores. There was no effect of side ($F_{1,42} = 0.53, p > .10$), although there was a side x craving two-way interaction ($F_{2,42} = 5.15, p < .01$), reflecting the fact that the groups had different patterns of asymmetry, as well as a side x valence x craving three-way interaction ($F_{2,42} = 5.15, p < .01$) demonstrating that these asymmetries were valence-specific. The two-way interaction demonstrated that the low craving group generally showed positivities shifted over the RH, while the medium craving group showed them shifted to the left for some stimuli, and few asymmetries were noted for the high craving group. Paired t-tests were used to probe the exact nature of the three-way interaction. The only significant differences were found in the low craving group, which demonstrated that amplitudes were significantly higher on the right for the negative stimuli ($t = 2.79, p < .05$), and significantly lower on the left for the neutral stimuli ($t = 2.74, p < .05$), with no effect for positive stimuli ($t = 0.73, p > .4$). Both of these comparisons met the Bonferroni-corrected significance level of .0167. No significant effects were noted for the medium or high craving groups, although the brainmaps reveal that the pattern of effects is actually different for the medium craving group, who showed increased positivities (rather than negativities) to the neutral stimulus. In general, the fewest lateralization effects were noted for the high craving group. These interactions are displayed diagrammatically in Figures 5.33a-c for the low, medium, and high craving groups, respectively.

Finally, for the *P3b* analysis, the 7 x 3 ANOVA revealed no main effect of craving group ($F_{2,42} = 1.09, p > .10$). There was a main effect of stimulus ($F_{2,84} = 6.60$, GG epsilon = .866, $p < .01$), electrode group ($F_{6,252} = 46.09$, GG epsilon = .348, $p < .001$), and their interaction ($F_{12,504} =$

4.55, GG epsilon = .459, $p < .001$), but no interactions involving the craving variable. The interaction reveals the slightly more parietal locus of the positively-valenced stimuli, as seen most clearly in the medium and high craving groups (Figures 5.31 - 5.32).

In the collapsed analysis, there was no main effect of craving group ($F_{2,42} = 1.72$, $p > .10$). There was no significant effect of side ($F_{1,42} = 0.08$, $p > .10$), nor did the side x craving interaction reach significance ($F_{2,42} = 2.49$, $p < .10$). There was again a significant effect of valence ($F_{2,84} = 4.34$, $p < .05$), as well as a significant side x valence interaction ($F_{2,84} = 3.99$, $p < .05$), as described above. Again, no interactions with craving were noted.

Problems and Limitations

There were certain problems and limitations with the experimental design, equipment used, and with methods of data collection that warrant further discussion.

Experimental Design

Since individuals were not compelled to press the button (place a bet), but were rather told to try to win as many points as possible, some individuals appeared to bet only during the initial blocks of the task. This potential problem was confounded by the fact that, being a relatively long and arduous task, some individuals appeared to simply give up. This resulted in problems of interpretation (it is unclear whether individuals did not press the button as a specific strategy, or whether they had abandoned the task). At the same time, it also presented problems in terms of analysis, as responses could not be broken down by response-contingency as there were not always enough responses per category to average together. That is, if an individual elected *not* to place a bet, and then learned he would have lost points in the event that he had placed a bet, his reaction should be a positive one (relief). However, since cues were broken down solely into the 5 cue categories - rather than cues as a function of response-type - some of this information was lost. Due to the tendency of subjects to give up during the latter half of the task, sufficient trials could not be obtained for this subanalysis. Future studies should bear this problem in mind. Specifically, using the probabilities as outlined by Bechara et al. (1996) appears to necessarily result in an overly-long ERP task. Balance between the factors of task duration *vs*. obtaining a large enough trial *n* for each condition subtype is an important consideration.

Another significant consideration regarding this task is that it is a novel modification of the Bechara et al. (1996) gambling task. As such, it has not been previously tested with ERPs, and so results were, to some extent, unpredictable. For instance, our data failed to elicit a P3a component, which was unexpected given the nature of the task (e.g., the unpredictability and salience of the high-risk cue). At the same time, group differences in early components (N170 and P220) were not anticipated, and were therefore difficult to interpret.

Methods

Our method of decreasing impedances by wetting the scalp - although approved by engineering staff at EGIS - does run the risk of saltbridge connections between neighbouring electrodes. While these are likely temporary, the reader should be aware of this problem.

Software Limitations

The EGIS software also has some constraints that inherently limit the effectiveness of the data presentation.

EEG. The EGIS system does not automatically output voltage indicator/timeplot bars, as is typically presented in ERP studies. The waveforms presented herein were generated manually outside of EGIS, using SPSS to perform averaging operation and Excel for display purposes.

Brainmaps. In terms of brainmaps, only four columns of maps can be presented at once using the EGIS equipment, and so our presentation of the five cue types was hindered. Nor does the software automatically output a colour bar enabling one to see the full range of values.

Data and Analysis Considerations

For analysis of the ERP data, we collapsed data from 128 electrodes to 7 electrode groups, in effect creating 7 "super-electrodes". While this was helpful from an analysis standpoint, it obviously resulted in a loss of information. For publication purposes, more complex analyses (such as a principal components analysis of information from all sites over all timepoints) would be preferable.

Additionally, our method of picking the peak amplitude within a given latency window can produce inaccuracies if, for example, the highest amplitude within the window is found at the edge of the window. A different analysis, such as mean amplitude within the window, could assuage this problem.

Finally, our use of an average reference, although conventional, can create problems in terms of waveform interpretation. Voltage measurements reflect differences in potential between any site and some reference site. The assumption when using an average reference is that when the surface of the head is sufficiently sampled the positive and negative fields will "sum to zero". Although this does not account for the underside of the head, the EGIS program attempts to correct for this by prforming a "polar average reference effect" correction. However, it is also clear that different regions of the scalp can, at any given time, actually best reflect the "average" activity. This can make interpretation of the brainmaps particularly problematic. Conversely, when using an "inactive" reference (e.g., tip of the nose, or mastoids) the site that the rest of the brain activity is being compared to, for all practical purposes, shows *no* activity - however, neither is this method indisputable. At any rate, our use of an average reference must be considered when examining our results.

Discussion

Behavioral Effects

Speculatively, the increased behavioural output to the first block of trials may be considered an enhanced response to novelty. This has been reported in animal studies of drug abuse (e.g., Prasad et al., 1998), and similar effects were observed in spontaneous skin conductance responses following a priming dose of alcohol (Laberg and Ellertsen, 1987). It is also in agreement with the results of several studies showing increased orienting reflexes in high sensation seekers to the initial presentation of a series of visual or auditory stimuli (Zuckerman, 1990). Self-reported craving has been shown to decrease over experimental trials (Dols et al., 2002), suggesting the behavioural and subjective habituation effects may be related. A parallel effect is described in Chapter 6, in the initial trials of the Controlled Word Association Test, confirming that the response is specific to novel situations.

Among cocaine addicts, disadvantageous decision-making was correlated with frequency of use. No relationship, however, was found with quantity consumed. Neither relationship was found with alcohol, in contrast to Mazas et al. (2000), who found a relationship between decision-making and quantity of alcohol consumed. Task differences may have contributed to the discrepancies in our findings.

The hypothesized relationship between craving and high-risk behaviour over the course of the task was not substantiated. In fact, the low craving group showed the largest behavioural increases to high-risk stimuli over the course of the task. While this finding is counterintuitive, it may reflect the fact that the high craving group had an altered reaction to reinforcers, as indexed by deficient lateralization to valenced reinforcers; that is, a learning deficit - evident in the low craving group - may have been present in the higher risk groups, but masked by their relative inability to react to penalties.

Difference in Number of Artefact Free Trials

Unexpectedly, a difference was observed between the number of acceptable ERP trials obtained for stimuli of different valence. For both cues and reinforcers, positively-valenced stimuli were most likely to be artefact-free. However, among cues this difference was not significant, whereas among reinforcers the positively-valenced and neutral stimuli were significantly more likely to be artefact-free than the negatively valenced stimuli. The exact pattern appeared to be dependent upon craving severity.

This may result in some decreased reliability among the "risky" trials, and the trials that were punished rather than rewarded, although mean *n*'s for these stimuli were still high enough to make the resultant waveforms relatively stable. One might speculate that this effect may reflect an involuntary startle response to stressful stimuli. Alternately, it could also be reflective of Damasio's (1994; discussed in brief in Krawczyk, 2002) somatic marker hypothesis, which claims that ventromedial PFC regions reactivate bodily states, biasing behaviour to risky events. However, this interpretation would suggest that acceptable cue trials should vary as a function of damage to the region, suggesting risky trials would be rejected more often with increased craving severity, a finding which our results did not verify.

Electrophysiological Results

While the task specifications led us to anticipate a P3a effect, none was evident in this study. This may in part reflect the fact that the stimuli (even the high-risk stimulus) were not novel to the subject, although they *were* likely salient. It is important to understand that in a novel and untried paradigm one cannot be certain which waveforms will be elicited, and expectation of a clear P3a wave may not have been reasonable.

The most important finding in this study was the direct relationship between N170-P220 amplitude and craving severity in response to "risky" cue stimuli. The high craving group showed a deficit in their response to high-risk stimuli, as evidenced by their decreased N170-P220 amplitude, while the low craving group showed the most preserved N170-P220 amplitude range. Responses were intermediate for the medium craving group. These results confirm the prediction of decreased amplitudes being related to craving. These findings extend previous work showing decreased amplitudes in alcohol (Hada et al., 2000; Rodriguez Holguin et al., 1999) and cocaine abusers (Biggins et al., 1997), by demonstrating that decreased amplitudes are also seen *within* dependence groups, and are associated with level of craving. However, in those studies, it was most typically later components (e.g., the P3a and P3b) which showed amplitude reductions, rather than earlier exogenous components. However, it has been observed that the N100 "is sensitive to both the physical properties of the stimulus as well as to *the nature of the interaction between the subject and the event*" (Fabiani et al., 2000; italics added).

Given this perspective, it is tempting to speculate that these components illustrate differences in automatic processing of affective stimuli. Halit and co-workers (2000) found that the N170 was larger for unattractive, atypical faces with no effects on the P2, while artificial alteration of features increased P2 amplitude. Moreover, the P2 effect was significantly larger over the RH. These results suggest that the N1 and P2 may play a role in automatically alerting the individual to potentially atypical, unattractive stimuli in the environment. The fact that these stimuli carry potential evolutionary value (i.e., in reproductive terms) suggests that automatic perception of disfiguration may be useful; interestingly, the same may be said of potentially "risky" stimuli. As our study found a reduction in these waveforms related to craving, it is suggested that the perception of affective valence may be altered as a function of dependence, perhaps as a biproduct of decreased attentional capacity. Because these effects were specific to high-risk cue stimuli, and because they vary with craving severity (which may reflect functioning of ventromedial PFC regions), they may represent an ERP correlate to the anticipatory skin-conductance responses found by Bechara and colleagues (1996) in their gambling task, although this is speculative. At the least, these results suggest a deficit in learning aversive contingencies among individuals with severe cravings.

Other studies have also reported alterations of these early waveforms to processes and issues relevant to addiction. For instance, Yee et al. (1992) found that the N1-P2 peak-to-peak measurement to auditory stimuli was smaller in dysthymic, as compared to anhedonic subjects or normal controls. The authors suggested this may be related to decreased attentional resources for this group. Because craving seems to be associated with depressive symptomatology (see Chapter 4), one may posit an association between these early waveforms and craving. Interestingly, a study of visual attention, assessing global/local feature selection, found larger amplitudes of the N1 and P2 when spatial attention was directed to the left rather than right visual field (Han et al., 2000), as well as larger P2 effects for global rather than local stimuli. Taken together with the findings of Yee et al.'s study, these results suggest a dominance of the RH in modulation of the N1-P2 complex as a function of attentional allocation. If RH dominance in attentional allocation is correct, it may be reasonable to expect these early waveforms to vary as a function of addiction, in which the RH appears to be compromised. Indeed, Cohen et al. (2002) noted decreased amplitudes of the visual N1 in abstinent alcoholics. These authors also noted topographic asymmetries in the alcoholics not present in the controls, although the exact latency at which this difference occurred was unclear. These authors found amplitude reductions over the LH, an effect predicted by our model for abstinent individuals showing RH recovery.

Somewhat longer latency waveforms appear suggestive of similar processes. Pliszka and co-workers (2000) demonstrated decreased amplitudes of a right-lateralized N200 waveform in an ERP assessment of ADHD children. The authors believed this attenuation to be consistent with the notion of a deficient "response inhibition signal", comparing it to the children's metaphorical inability to voluntarily "hit the brakes". Decreased N170-P220 amplitudes in this experiment may represent a similar difficulty. Hill and co-workers (1995) found a smaller range in the amplitude of the N250 in alcoholics or the brothers of alcoholics, compared with matched controls. However, these authors interpreted their results as suggesting poorer modulation to changing probability conditions by the affected groups, as suggested by Kirino et al. (2000), an explanation which does not fit these data as all five cues in this task were equiprobable. It is worth considering, however, whether alterations in amplitude may have been related to *subjective* probability effects; that is, the possibility that some cues seemed to occur more often, to some groups. This question is open to experimental verification. Kotchoubey and co-workers (1997) attempted to dissociate expectancy as determined by objective probability from expectancy related to what the subject hoped would occur. The task bears similarities to the one performed herein, as it involved cues which were either predictive (80% correct) or non-predictive (50% correct), to events that were either likely (71% probability) or unlikely (29% probability). Individuals were told they would win money for betting on events that were not cued, thus risk-taking behaviour was rewarded. Invalid cues resulted in larger P3b waves, as predicted by the typical notion of expectancy influencing P3b amplitude, but these results did not seem to depend upon conditional probabilities. In fact, the low probability non-cued event had a significantly larger amplitude, despite equiprobability to the low probability cued event, and the high probability non-cued event. Hence, the cue as objective predictor had a different impact than the subject's actual prediction; as the authors note, a mismatch between the cue and reinforcer was less important than a mismatch between the reinforcer and the subject's behaviour, as only behaviour influenced their possibility of gain. In this context, however, it is important to note that we found no correlation between craving and amplitude of the P3b.

Aside from the decreased amplitudes in responses to craving, there were also lateralization effects. Individuals in both the low and high craving groups demonstrated positivities over the RH to the high-risk cues, with a concomitant left-lateralized negativity in response to low-risk (positive) cues. These results complement those of Kayser and co-workers (1997), who found an enhanced N2-P3 amplitude for negative stimuli over the RH. It is noteworthy that our stimuli differed significantly from theirs, in that ours were not intrinsically affectively-valenced (their study employed faces with dermatological diseases), but only acquired value following conditioned association with wins/losses. As in their study, the stimulus categories were equiprobable, and so stimulus probability cannot explain amplitude differences. Moreover, because our stimuli were comprised of five simple shapes, it is difficult to conceptualize differences in processing as arising due to stimulus complexity, attentional requirements, or recognition difficulty, all of which have been proposed as confounds in terms of lateralized processing (Kayser et al., 1997). The fact that lateralization for these cues was restricted to the low- and high-craving groups was unexpected. Recent imaging studies (London et al., 2004; Tankard et al., 2003) have suggested curvilinear effects of anxiety, suggestive of the familiar Yerkes-Dodson law (Yerkes and Dodson, 1908), which may have played a part in the responses to high-risk cues. The U- shape function was also suggested in the performance slope scores of the three groups (Figure 5.8).

LH lateralization of the N170 waveform to positive cues was only significant in the low craving group. That it was not significant in the other groups suggests that individuals with stronger cravings my have difficulties processing potentially rewarding cue stimuli. In fact, the high craving group showed the most significant lateralization to high-risk stimuli.

Different results were obtained for reinforcer stimuli. For reinforcers, the lack of lateralization in the high craving group may have reflected their inability to distinguish between stimuli of difference valence (wins *vs.* losses). Chung and co-workers (1996) administered a verbal task in which negative, positive, or incongruent endings were presented at the end of a sentence to both optimists and pessimists. While the data was not analyzed specifically to examine the effect, their figures reveal a lateralized positive waveform when optimists were presented with negative endings, an effect that was bilateral for pessimists. This implies that our high craving group was perhaps more "pessimistic" in terms of the potential for a positive outcome to high-risk stimuli in the task. This is in agreement with our finding that those with the highest cravings had a tendency towards lowest performance estimates.

Taken together, the results of the cue and reinforcer stimuli suggest that cravings are associated with a decreased ability to predict whether a goal stimulus will be of positive or negative valence, and a decreased response to valenced stimuli. These results confirm our hypothesis of deficient reinforcement-based learning processes in conjunction with craving.

Summary

Much of the electrophysiological research in substance abuse has focused on non-specific indices, such as the P3b, in the oddball paradigm; relatively little has focused on earlier components, which appear particularly sensitive to qualities that may be important in dependent, such as attention and attributions of stimulus salience. To this end, ERPs were recorded during presentation of a reinforcement-based learning task, to directly test the hypothesis of altered affective and expectancy mechanisms in craving. The task was altered to make it compatible with the collection of EEG data, and to capitalize on behavioural and cognitive difficulties in addiction. These changes included central positioning of stimuli, a forced rate of presentation, the addition of a "control" category, and monitoring of subjective level of performance.

Behavioural results were suggestive of a novelty effect, with behavioural activation as a function of craving was observed during the first block of trials. Unexpectedly, a valence effect was noted with regard to the number of artefact-free trials obtained, with positively-valenced stimuli generating the least artefact, perhaps reflecting a startle effect (i.e., blinking or movement) in response to punishment. Attenuation of the N170-P220 peak-to-peak measurement as a function of craving was observed in response to cue stimuli, in accordance with previous studies. These results confirm and extend findings of impaired inhibition capabilities as a function of craving. Surprisingly, given the task requirements, no P3a was evident. While there was in fact a P3b, it did not discriminate between craving severity groups. These may reflect alterations in subjective probability. Finally, decreased lateralization to reward/punishment stimuli was noted in individuals with the most severe cravings, potentially reflecting impaired affective processing.

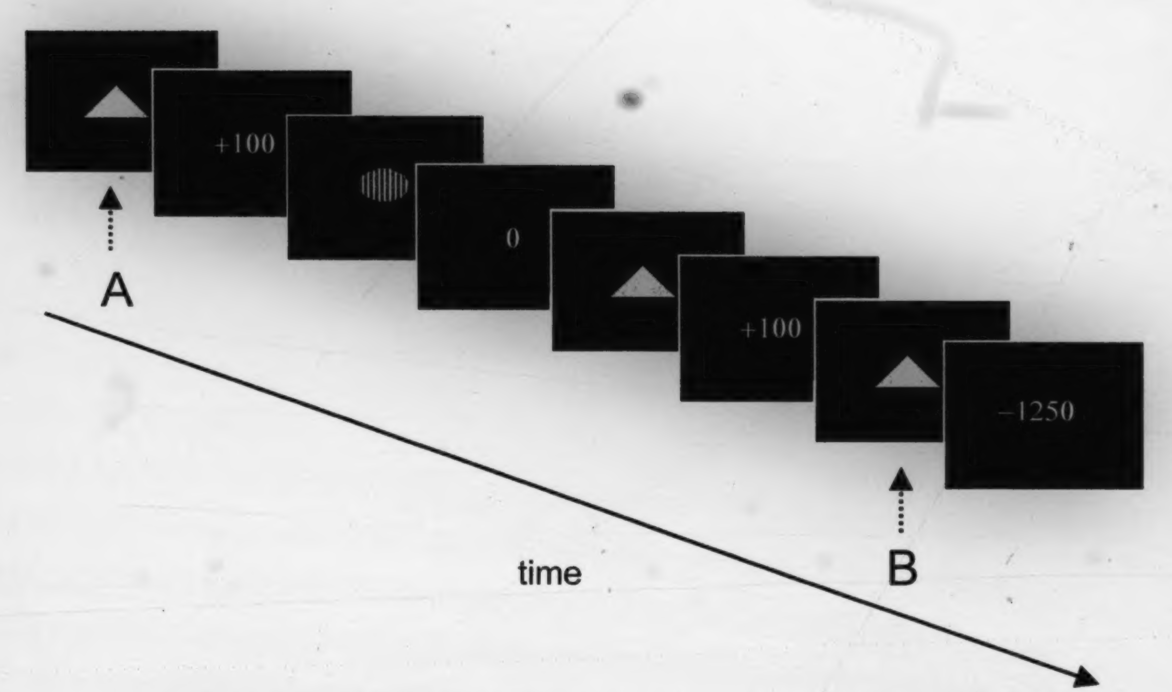


Figure 5.1 Pictorial depiction of the ERP task. Each shape cue is followed by a point reinforcer. Dotted arrows represent hypothetical "bets" (mouse clicks) in response to the high risk shape (the triangle) made by the subject. In A the subject wins 100 points; in B the subject loses 1250 points.

Stimulus Categories	Original Task (*n*=40/category; total n=160)		Revised Task (*n*=160/category; total n=800)	
	mean	**SD**	**mean**	**SD**
Deck A - Cue 1	-25	136.34	-25	135.05
Deck B - Cue 2	-25	379.78	-25	376.18
Deck C - Cue 3	+25	28.31	+25	28.04
Deck D - Cue 4	+25	75.96	+25	75.24
Control - Cue 5	*N/A*	*N/A*	0	69.82
Overall	**0**	**205.37**	**0**	**185.86**

Table 5.1 A comparison of the means and standard deviations of the stimulus categories from Bechara et al.'s (1996) original task and the ERP task used for this study.

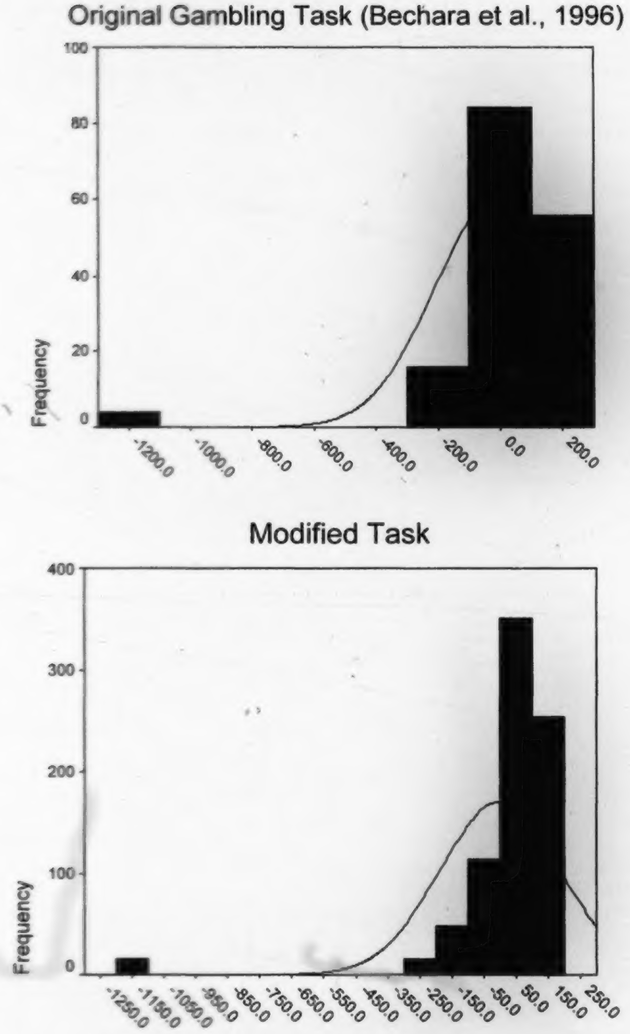
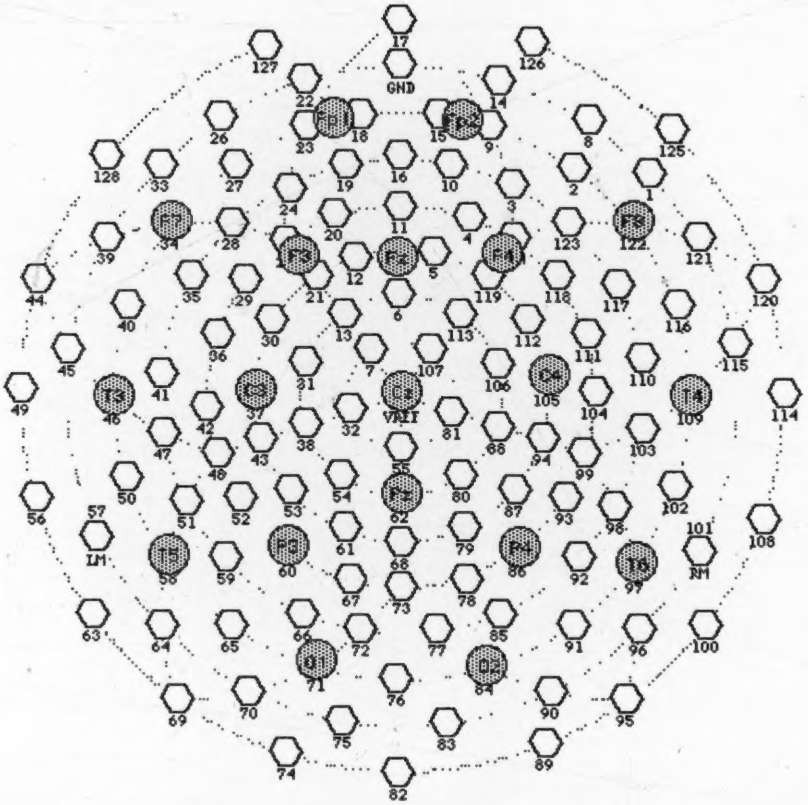


Figure 5.2 Comparison of the histograms for Bechara et al.'s (1996) original task and the ERP task presented to the subjects in this study.


17
127
126
GND
22
14
Fp1
Fp2
26
18
15
9
8
125
23
128
33
27
19
16
10
2
1
24
3
F7
28
20
11
4
123
F8
39
34
F3
Fz
F4
122
121
44
35
29
12
5
119
118
117
120
21
6
40
113
112
116
30
13
111
36
115
45
7
107
110
C3
Cz
C4
106
T3
41
37
31
T4
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114
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VREF
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98
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101
108
61
79
T5
LM
P3
P4
T6
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60
68
92
58
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RM
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78
73
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96
100
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72
77
O1
O2
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Figure 5.3 A layout of the EGIS 128 channel geodesic sensor net. Traditional 10-20 electrode placement sites are overlaid (grey circles).

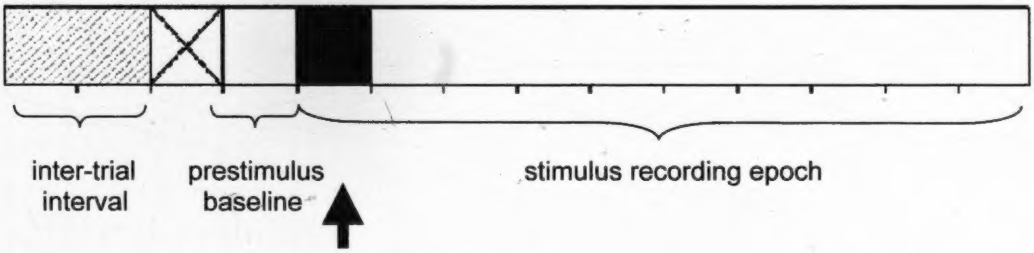
inter-trial interval
prestimulus baseline
stimulus recording epoch

Figure 5.4 Pictorial description of the recording epoch. Each tick along the horizontal axis represents 100ms. The arrow and associated darkened region denote stimulus presentation.

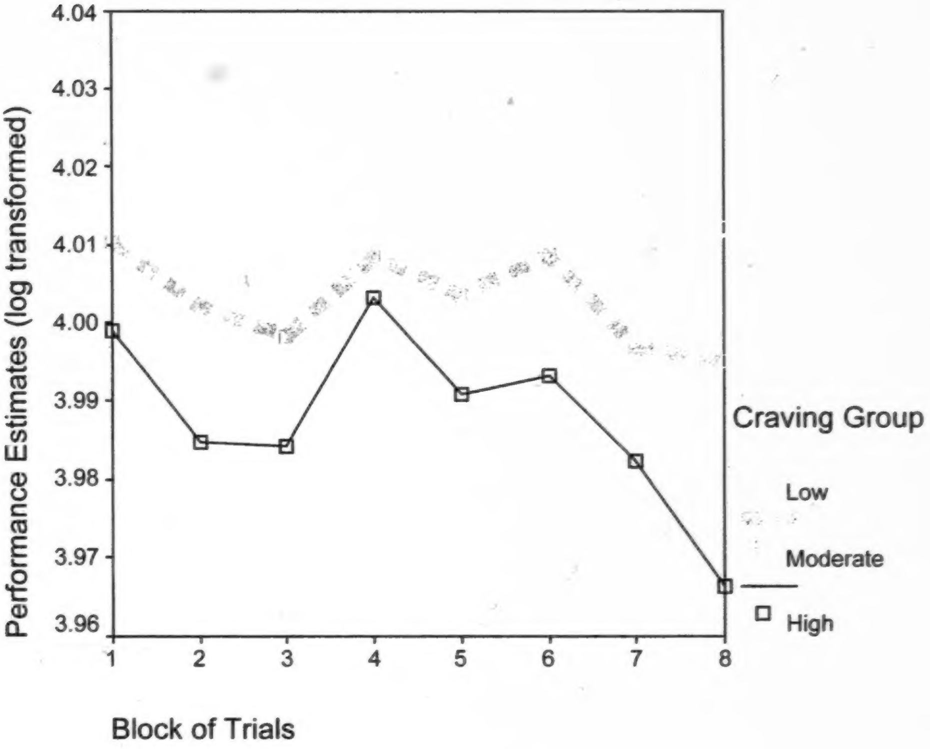

Figure 5.5 Trend towards decreased performance estimates associated with craving severity.

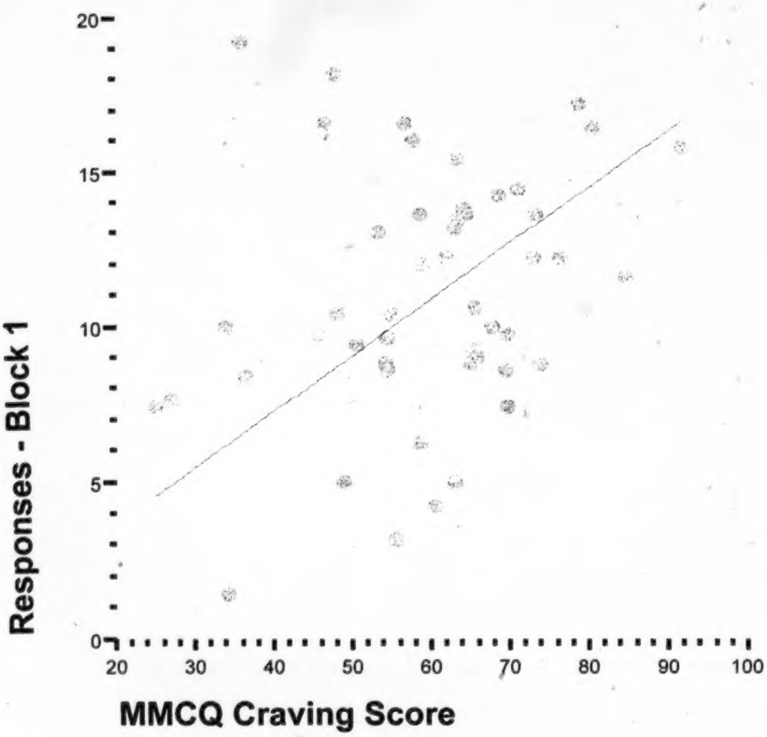

Figure 5.6 Regression line illustrating correlation between craving and enhanced responding during first block of trials.

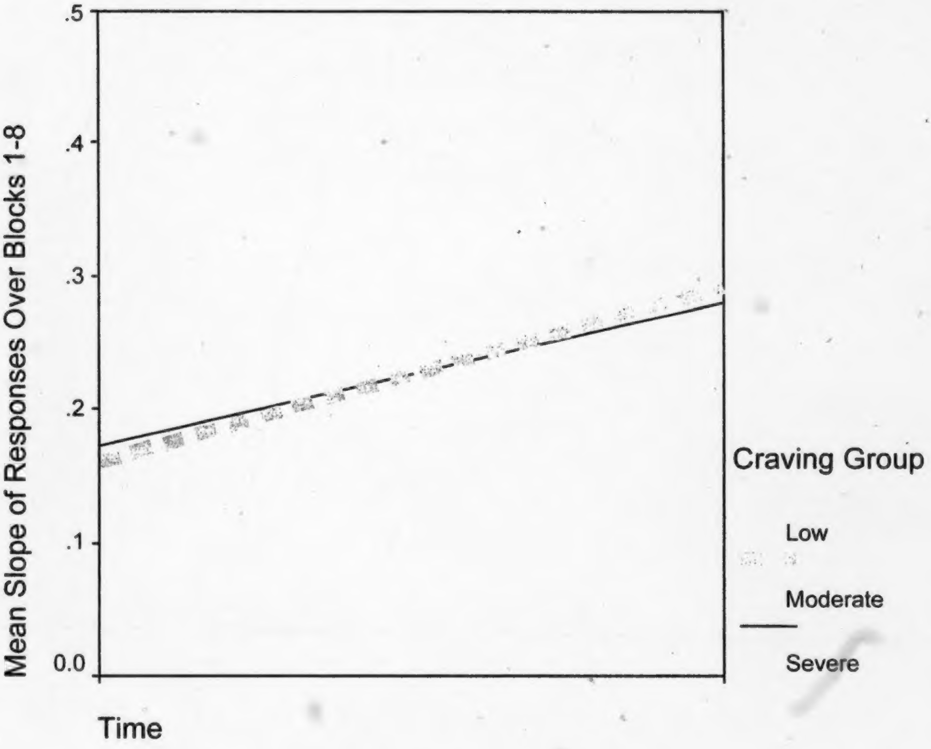

Figure 5.7 Response slope to the high risk cue, over time.

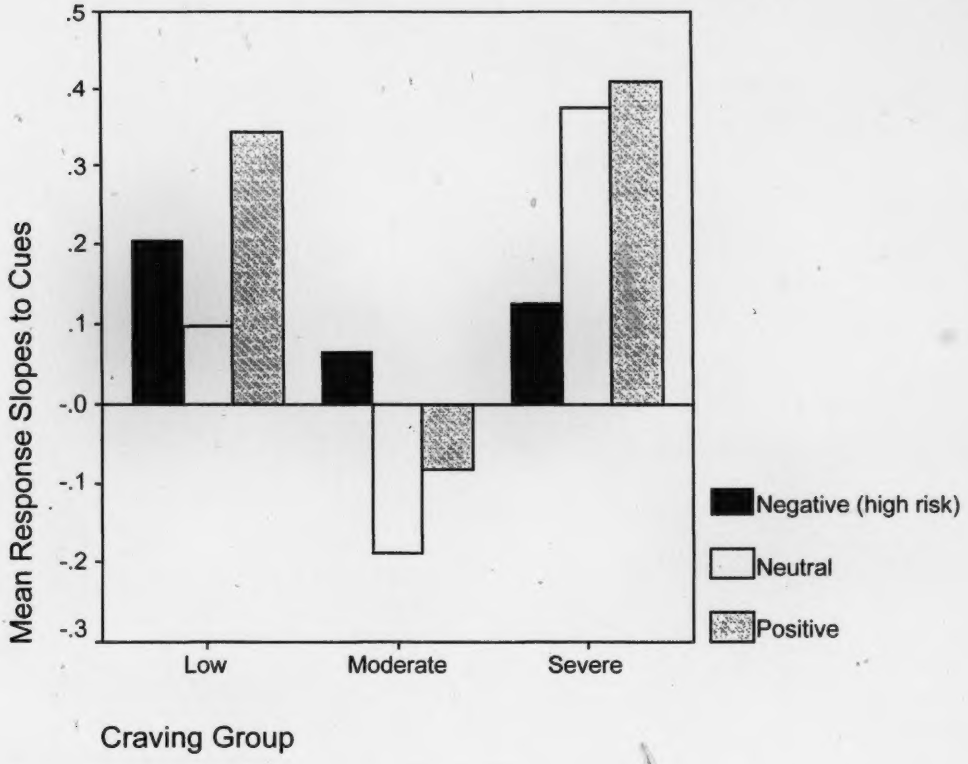

Figure 5.8 Overall responses to cue stimuli (by valence) as a function of craving severity.

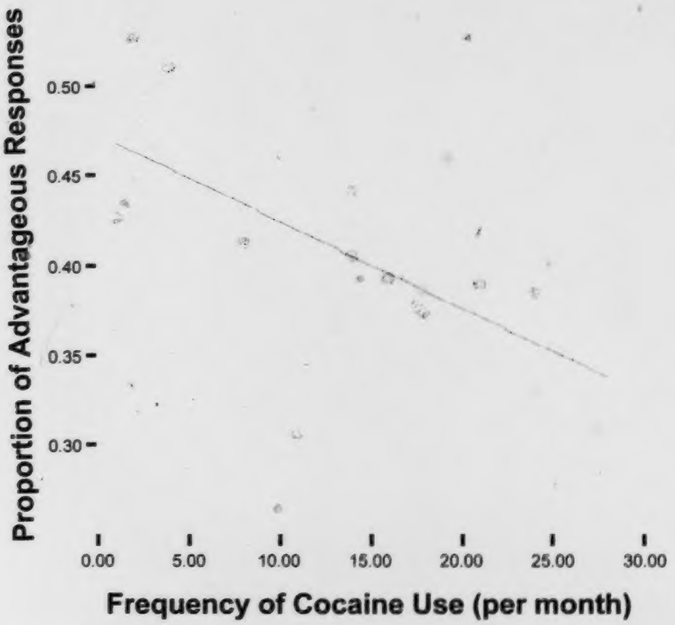

Figure 5.9 Regression line illustrating the correlation between disadvantageous responding and frequency of cocaine use.

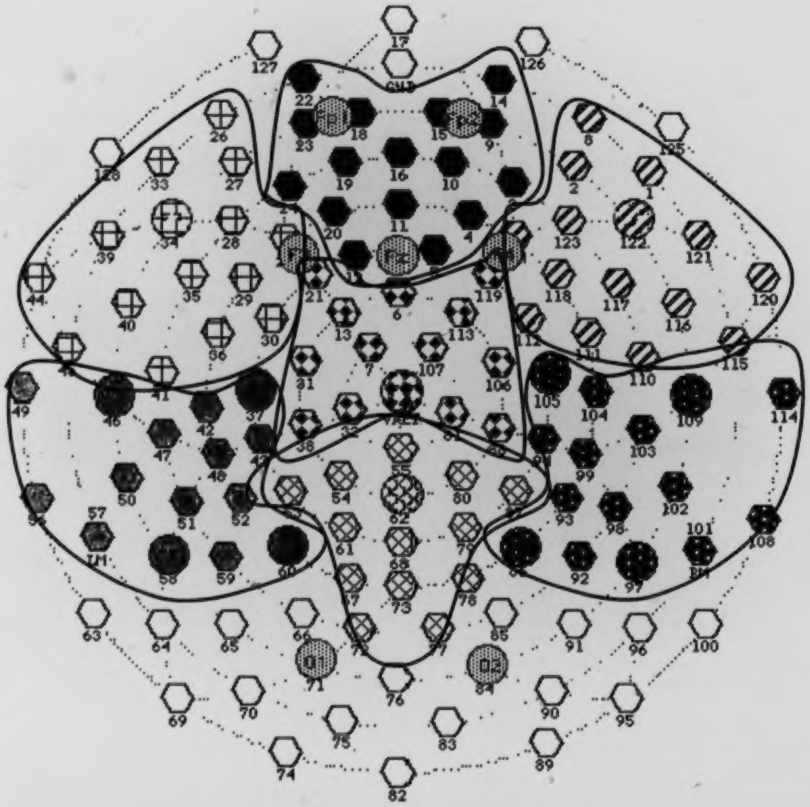
17
127
126
22
14
23
18
15
9
8
125
128
33
26
27
19
16
10
2
1
34
28
20
11
4
123
122
121
39
44
35
29
21
119
118
117
120
40
30
36
13
6
113
116
41
31
7
107
106
111
110
115
49
46
42
37
105
104
109
114
47
48
43
38
32
103
99
50
54
55
80
93
98
102
57
51
52
61
68
79
101
108
58
59
60
67
73
78
92
97
63
64
65
66
72
77
85
91
96
100
71
76
84
69
70
75
83
90
95
74
82
89

Figure 5.10 Subsets of electrodes used for analysis. Different fills are used to represent the frontal, centro-parietal, left lateral, and right lateral electrode subsets chosen for analysis. Subsets were chosen to be comprised of roughly the same number of electrodes (24-26). Electrooculogram (EOG) electrodes are excluded in order to reduce artefact contamination in the frontal regions.

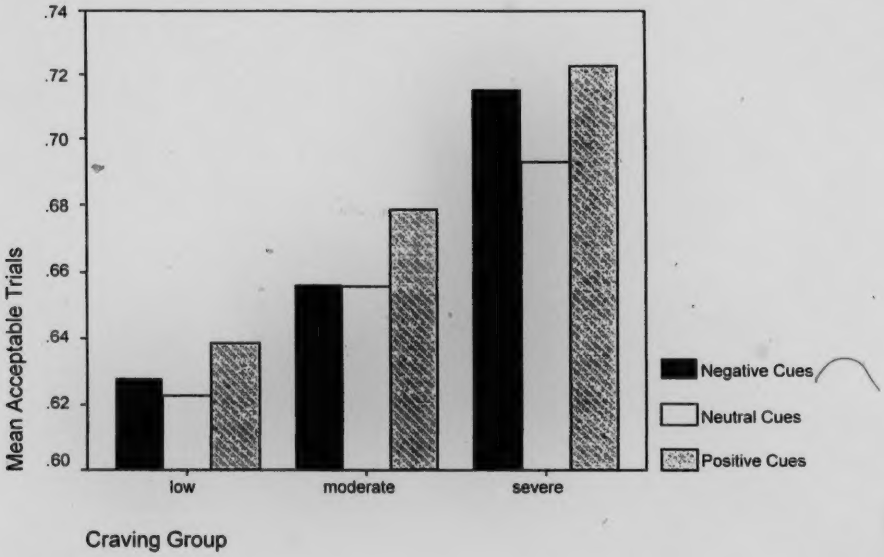

Figure 5.11a Difference in number of artefact free cue trials as a function of craving severity.

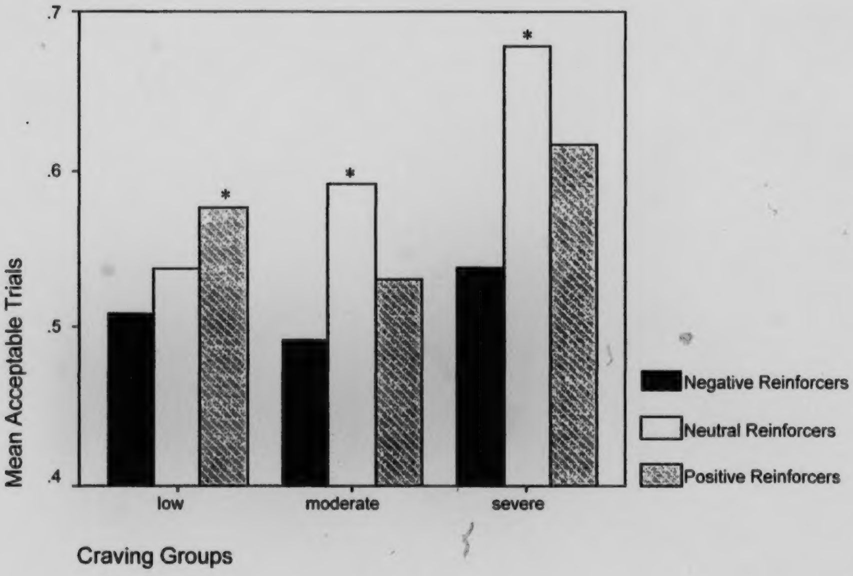

Figure 5.11b Difference in number of artefact free reinforcer trials as a function of craving severity.

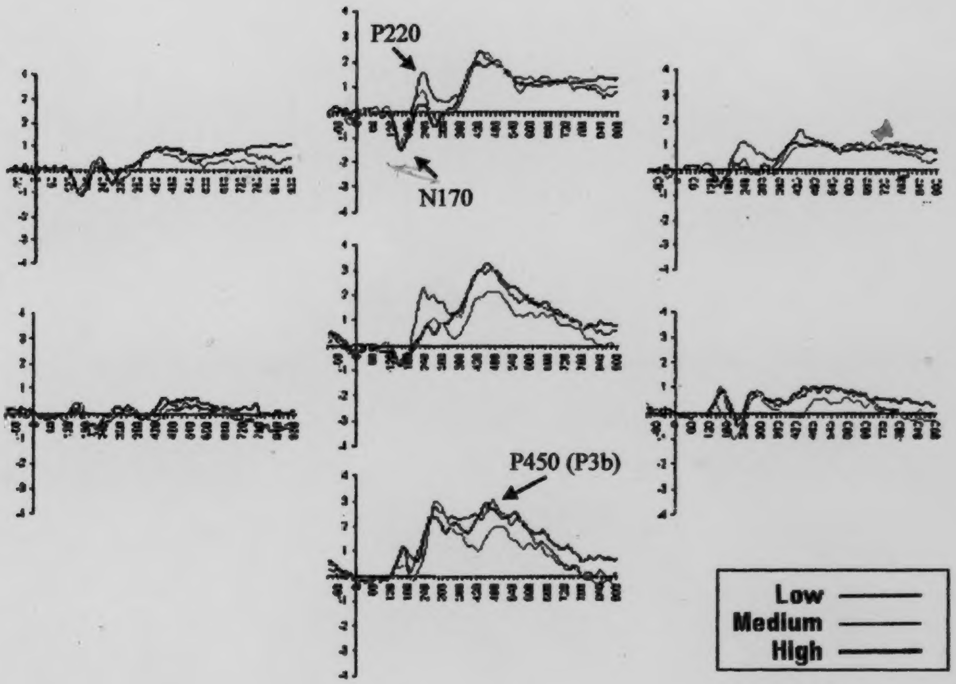

Figure 5.12 Responses of the three (low, medium, high) craving groups to the 1st cue stimulus - negative, low SD (low-risk). Data correspond to the 7 subsets of electrodes used in our analyses. All responses are with respect to the average reference. Units are in in msec along the x-axis; in uV along the y-axis. The N170, P220, and P3b responses are indicated for the reader's information.

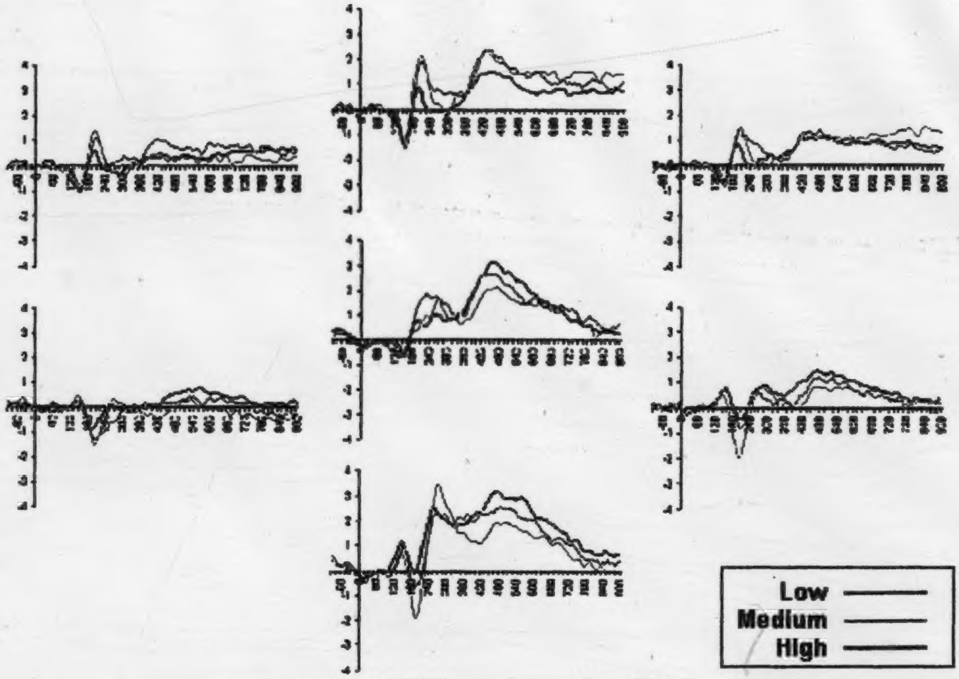

Figure 5.13 Responses of the three craving groups to the 2nd cue stimulus - negative, high SD (high-risk). Notice the attenuation of responses in the high craving group, particularly over the frontal regions. This attenuation may reflect differences in attentional capabilities.

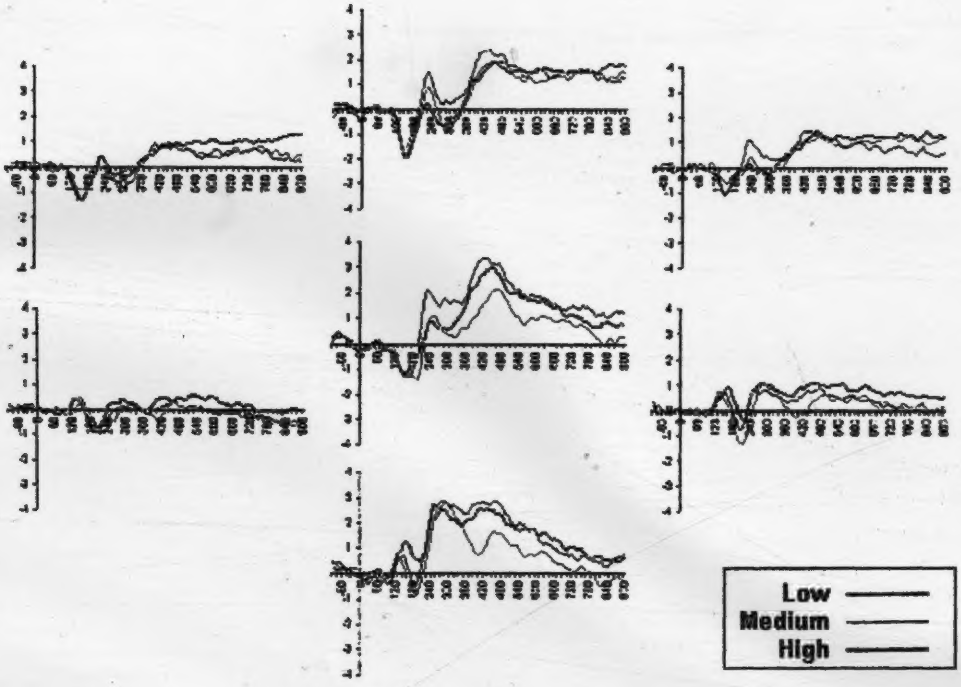

Figure 5.14 Responses of the three craving groups to the 3rd cue stimulus - positive, low SD (safest bet).

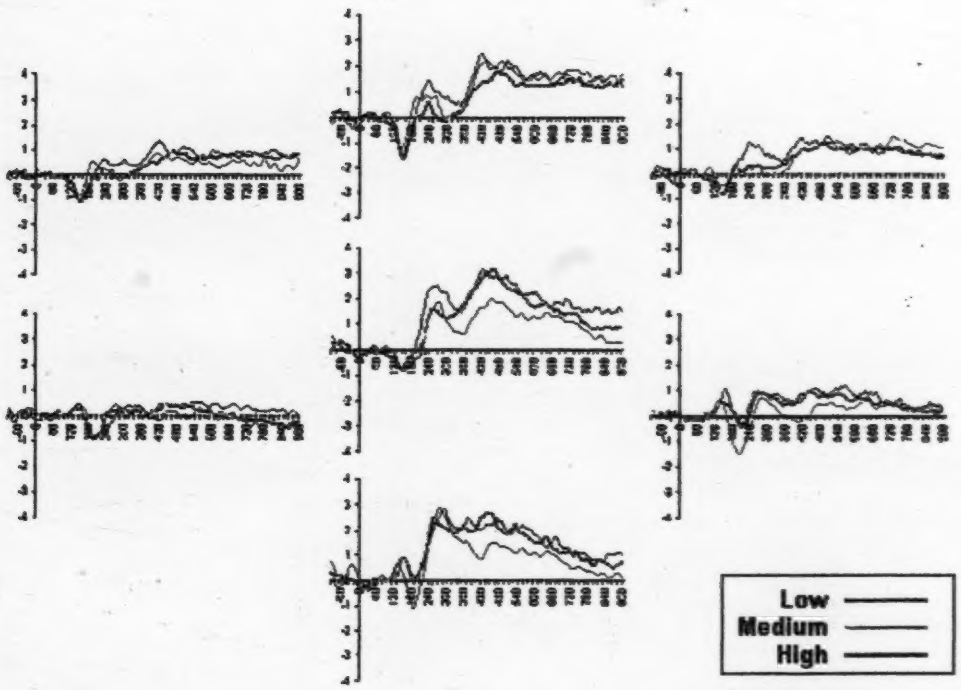

Figure 5.15 Responses of the three craving groups to the 4th cue stimulus - positive, high SD.

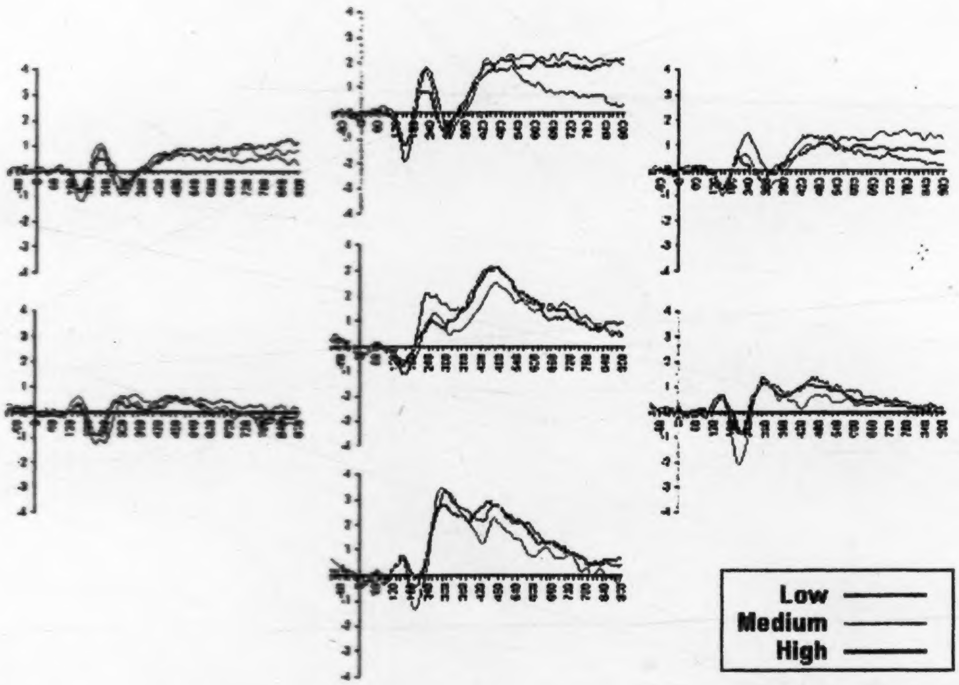

Figure 5.16 Responses of the three craving groups to the 5th cue stimulus - neutral stimulus (equal probability of wins/losses).

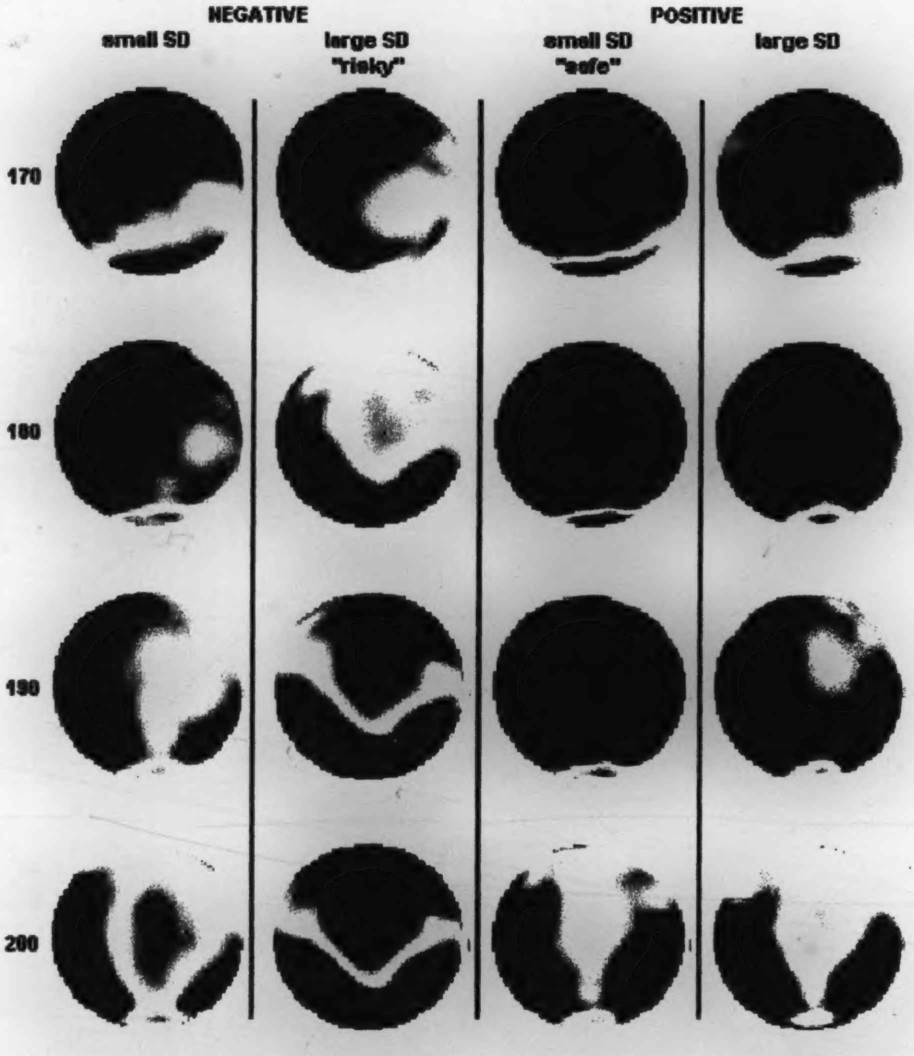

Figure 5.17 Cue responses in the low craving group from 170-200 ms following stimulus presentation. These maps translate the ERP values over each electrode into a color representation (positive = red; negative = blue; software does not output an accompanying color bar for range comparisons) at some timepoint. Rows display the average brain activity in 10ms increments over the timespan comprising the N170 - P220 response; time slices chosen to best illustrate differences between the cue types. Columns 1 and 2 represent negative cues (cues signaling potential loss following bets), with the second column being the "high risk" cue. Columns 3 and 4 represent positive cues (cues signaling potential gains following bets), with the third column representing the "safest" bet (smallest SD). The greatest overall positivities are observed in column 2, while the greatest overall negativities are seen in column 3. The neutral cue is not presented due to limitations of the software; however it generally bears a strong similarity to, and is not statistically different from, column 4.

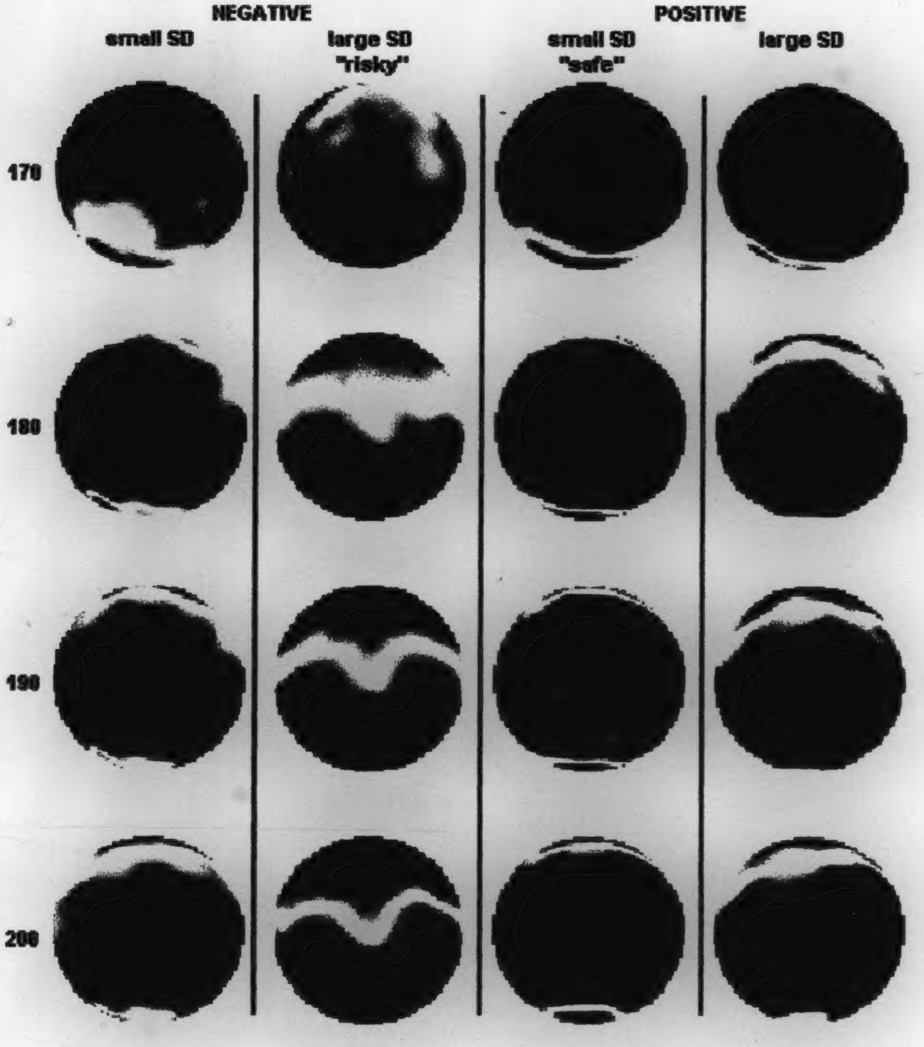
NEGATIVE
POSITIVE
small SD
large SD
"risky"
small SD
"safe"
large SD
170
180
190
200

Figure 5.18 Cue responses in the medium craving group from 170-200 ms following stimulus presentation. Displays data in same manner as presented in Figure 5.17.

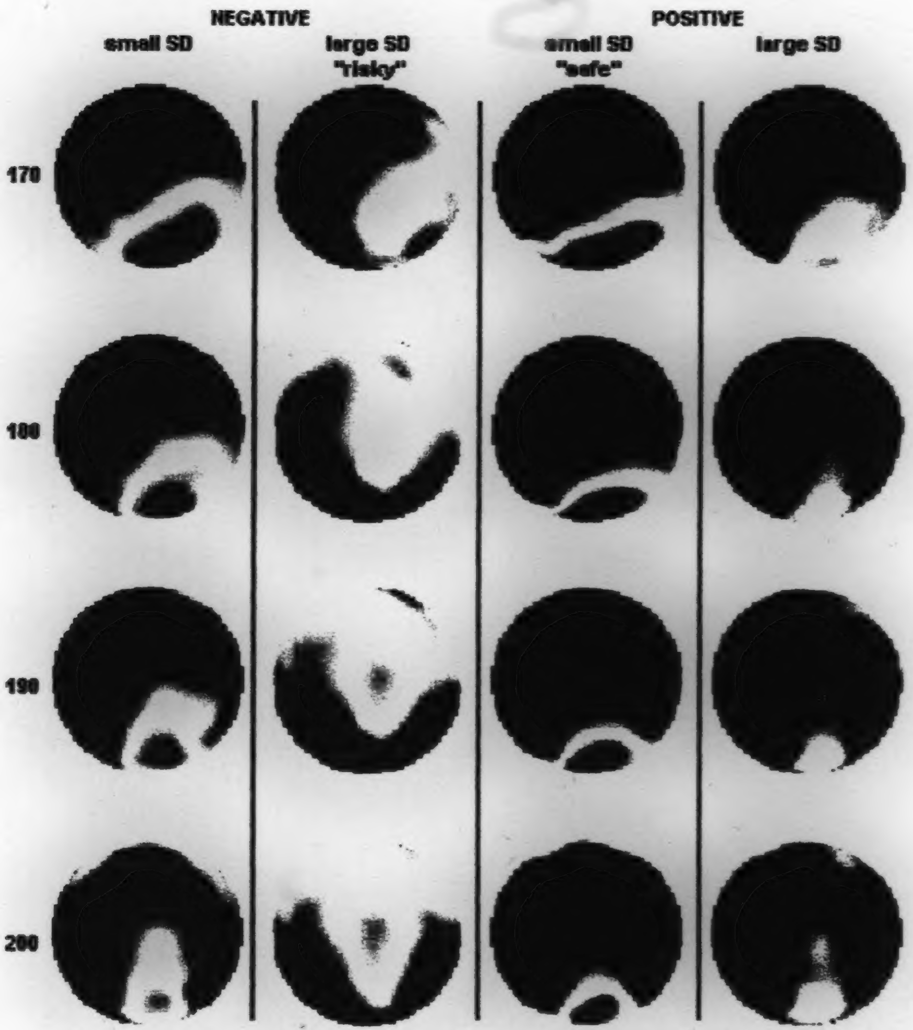
NEGATIVE
small SD
large SD
"risky"
POSITIVE
small SD
"safe"
large SD
170
180
190
200

Figure 5.19 Cue responses in the high craving group from 170-200 ms following stimulus presentation. Displays data in same manner as presented in Figure 5.17. Positive and negative amplitudes have been attenuated, in comparison to the other two groups.

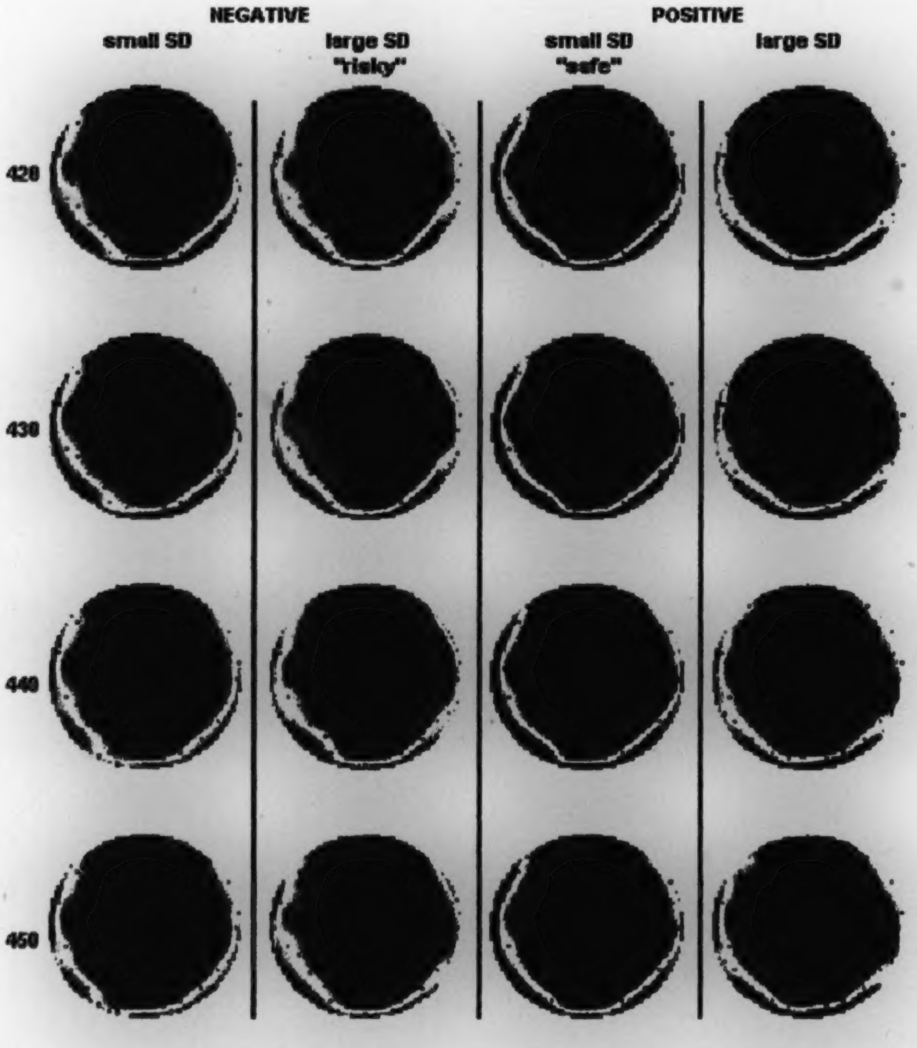
NEGATIVE
POSITIVE
small SD
large SD
"risky"
small SD
"safe"
large SD
420
430
440
450

Figure 5.20 Cue responses in the low craving group from 420-450 ms following stimulus presentation. Rows display the average brain activity in 10ms increments over the timespan comprising the P3b response; time slices chosen to best illustrate differences between the cue types (none observed). Columns 1 and 2 represent negative cues (cues signaling potential loss following bets), with the second column being the "high risk" cue. Columns 3 and 4 represent positive cues (cues signaling potential gains following bets), with the third column representing the "safest" bet (smallest SD). Note also the relative lack of discrepancies *between* craving groups (compare with Figures 5.21, 5.22).

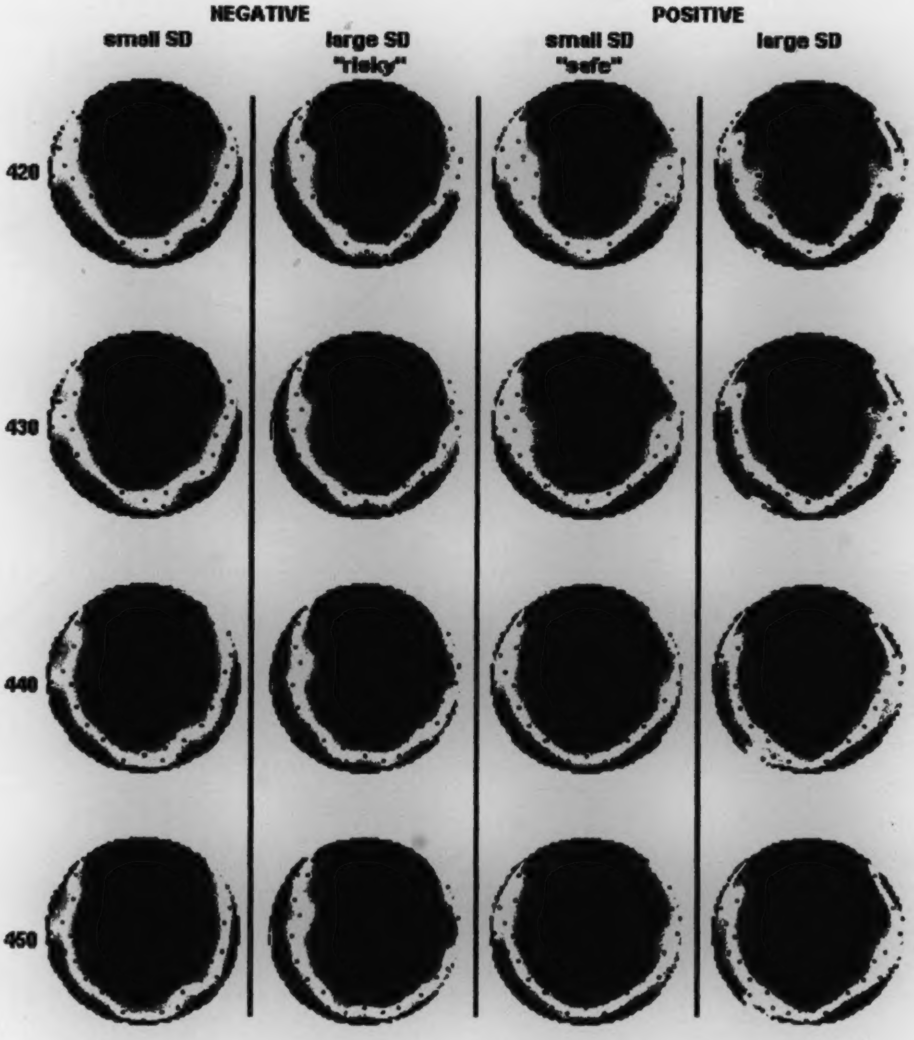
NEGATIVE
POSITIVE
small SD
large SD
"risky"
small SD
"safe"
large SD
420
430
440
450

Figure 5.21 Cue responses in the medium craving group from 420-450 ms following stimulus presentation. Displays data in same manner as presented in Figure 5.20.

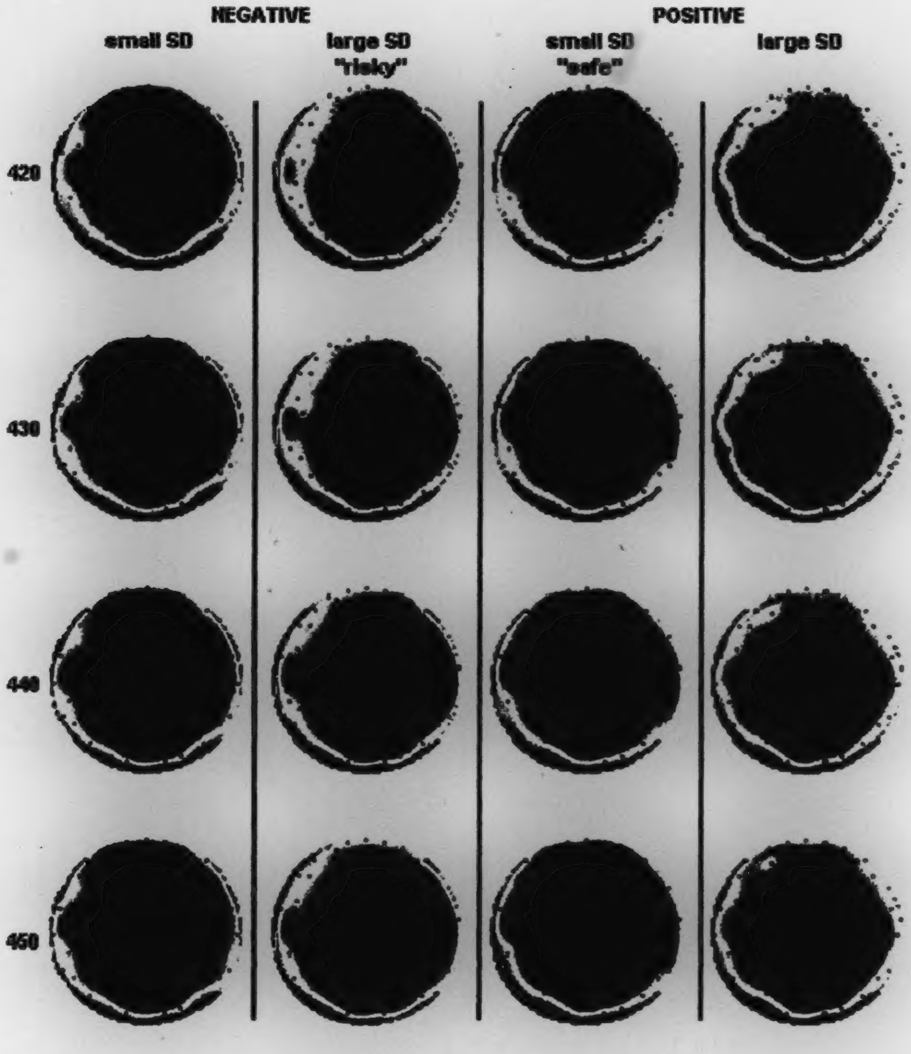

Figure 5.22 Cue responses in the high craving group from 420-450 ms following stimulus presentation. Displays data in same manner as presented in Figure 5.20.

		Component			
Variable	***df***	**'N170'**	**'P220'**	**'N170-P220 complex'**	**'P3b'**
7 electrode gps x 5 cue types					
CRAVING	2,42	2.43†	3.03†	**3.87***	0.23
STIM	4,168	**6.48*****	**6.90*****	***10.73*******	1.41
STIMxCRAVING	8,168	0.74	1.68	*2.02†*	0.59
ELECTRODE	6,252	***3.73****	***29.04*******	***28.50*******	***28.03*******
ELECTRODExCRAVING	12,252	*0.86*	*1.20*	*1.65*	*0.58*
STIMxELECTRODE	24,1008	***9.04*******	***5.56*******	***4.33*******	*1.71†*
STIMxELECTRODExCRAVING	48,1008	*1.03*	*0.66*	*1.27*	*1.04*
2 sides x 3 valences					
CRAVING	2,42	2.89†	1.96	**3.22***	0.07
SIDE	1,42	3.12†	**24.73*****	**14.96*****	**24.31*****
SIDExCRAVING	2,42	3.06†	2.73†	0.92	0.17
VALENCE	2,84	**12.00*****	**9.92*****	***25.53*******	1.81
VALENCExCRAVING	4,84	0.26	0.82	*1.11*	0.61
SIDExVALENCE	2,84	2.35	1.90	*0.07*	0.50
SIDExVALENCExCRAVING	4,84	1.07	0.18	*2.34†*	0.25

†<.10; *<.05; **<.01; ***<.001

Table 5.2 ERP amplitudes in response to cues. Scores are presented as F-values. (Greenhouse-Geisser corrected significance levels italicized)

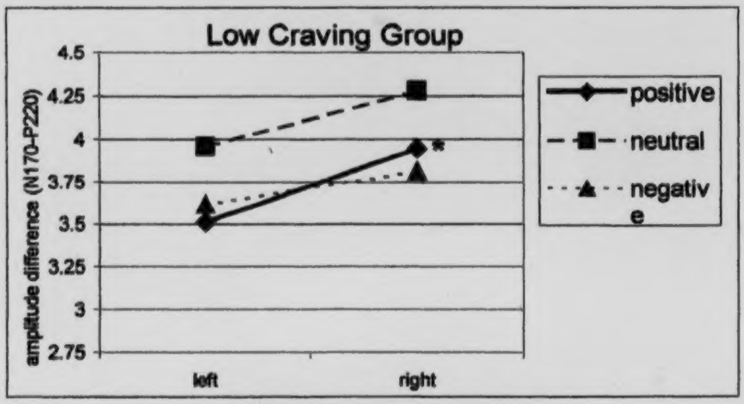

Figure 5.23a Interactions between cue valence and hemisphere in terms of amplitude range of the N170-P220 for the low craving group

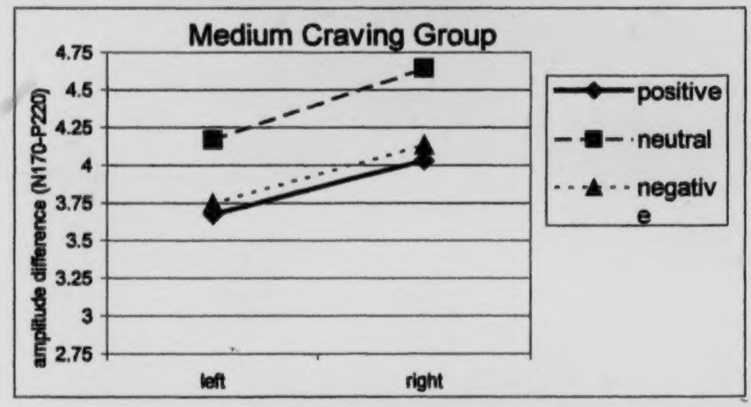

Figure 5.23b Interactions between cue valence and hemisphere in terms of amplitude range of the N170-P220 for the medium craving group

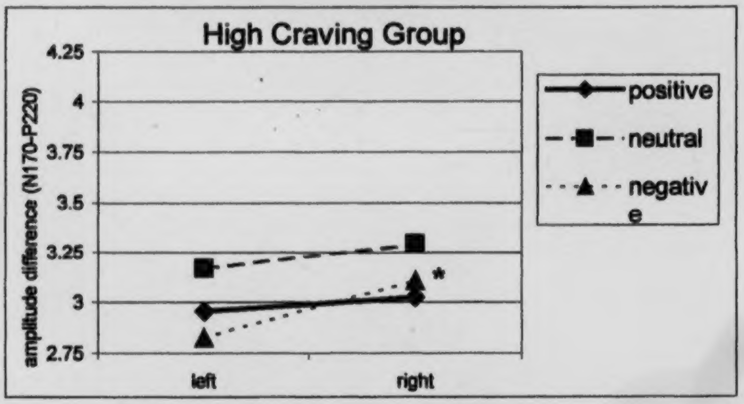

Figure 5.23c Interactions between cue valence and hemisphere in terms of amplitude range of the N170-P220 for the high craving group

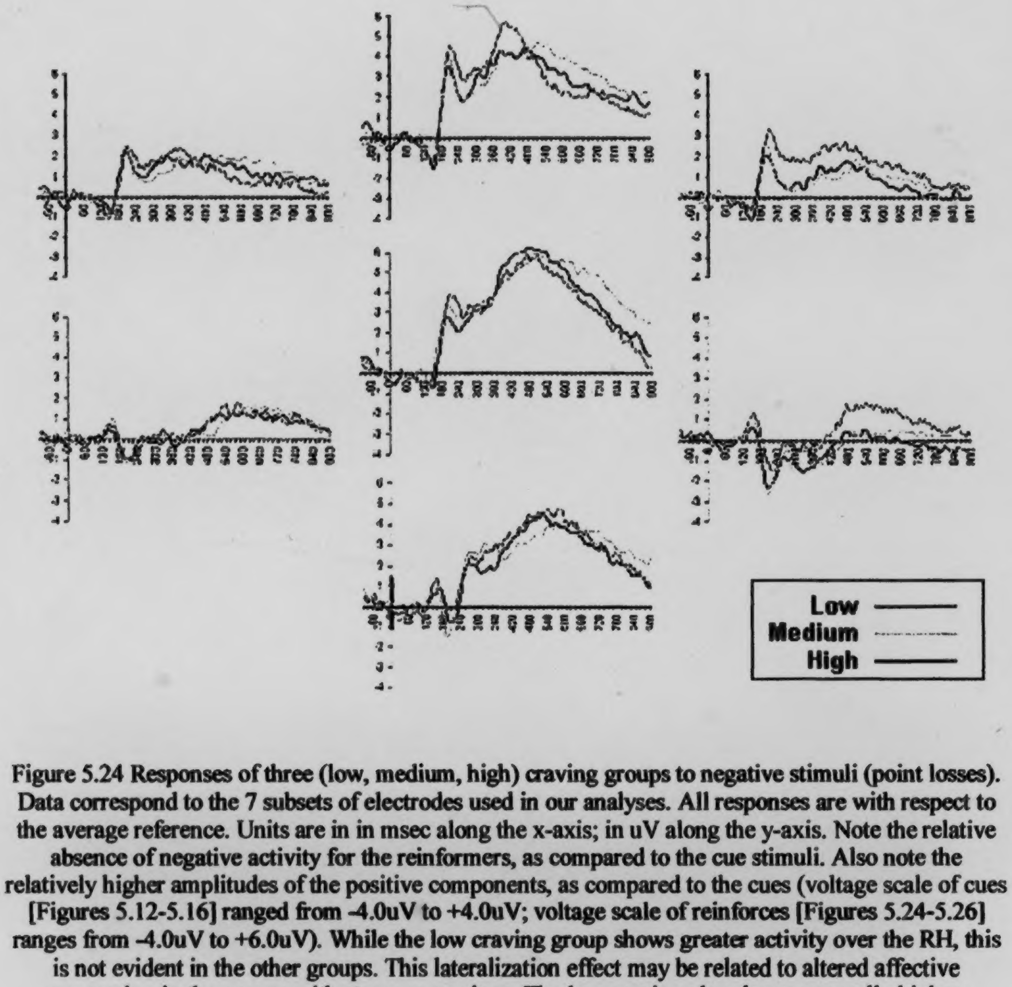

Figure 5.24 Responses of three (low, medium, high) craving groups to negative stimuli (point losses). Data correspond to the 7 subsets of electrodes used in our analyses. All responses are with respect to the average reference. Units are in in msec along the x-axis; in uV along the y-axis. Note the relative absence of negative activity for the reinformers, as compared to the cue stimuli. Also note the relatively higher amplitudes of the positive components, as compared to the cues (voltage scale of cues [Figures 5.12-5.16] ranged from -4.0uV to +4.0uV; voltage scale of reinforces [Figures 5.24-5.26] ranges from -4.0uV to +6.0uV). While the low craving group shows greater activity over the RH, this is not evident in the other groups. This lateralization effect may be related to altered affective processing in the groups with stronger cravings. The low craving also shows generally higher amplitudes across conditions (see also Figures 5.25, 5.26).

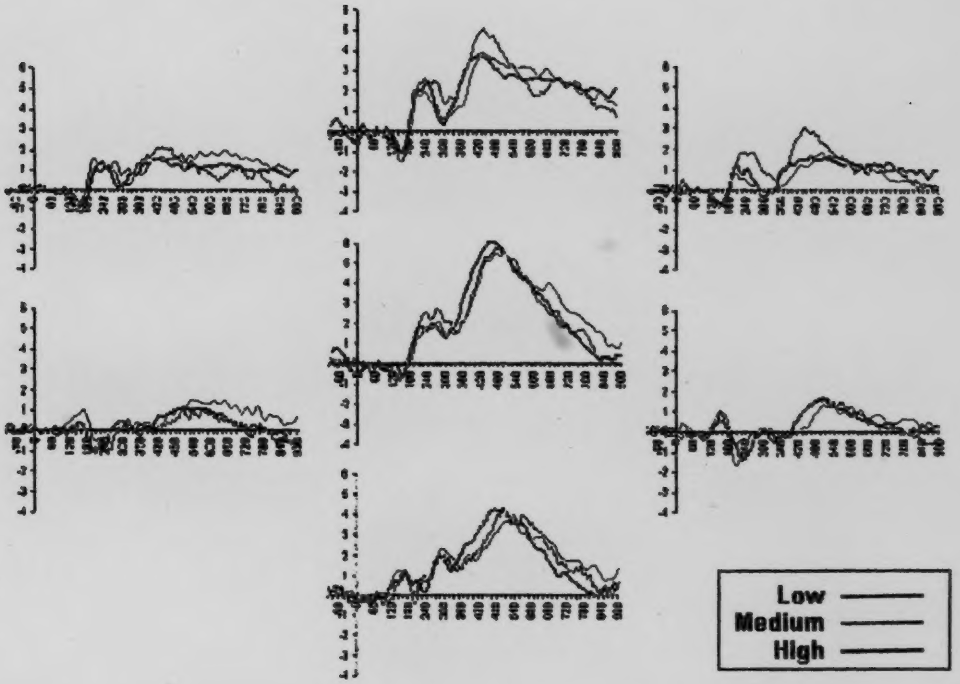

Figure 5.25 Responses of the three craving groups to neutral stimuli ("0" scores).

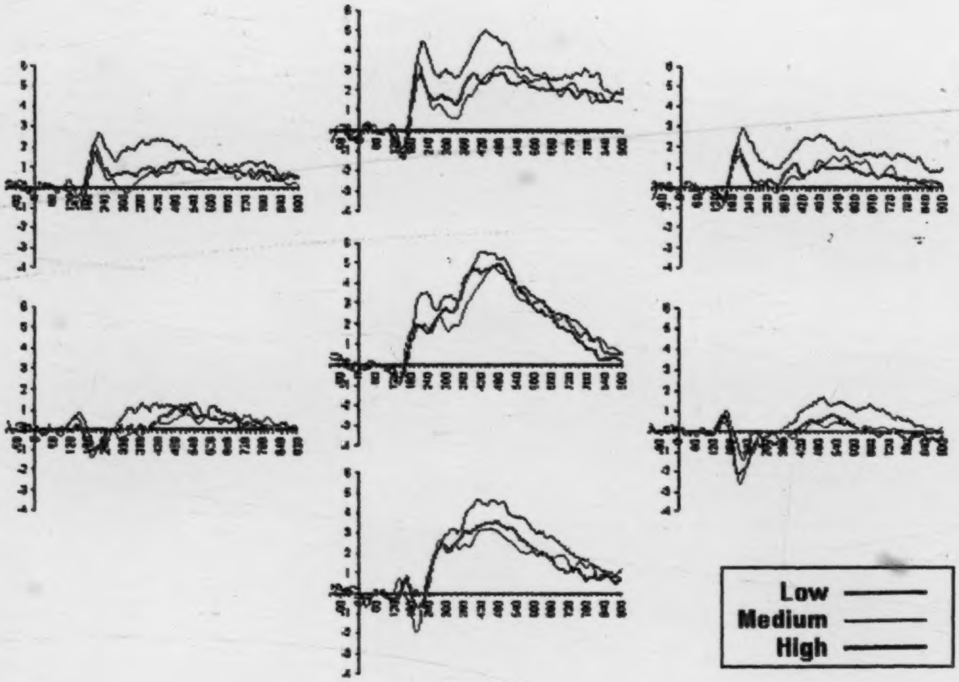

Figure 5.26 Responses of the three craving groups to positive stimuli (point wins).

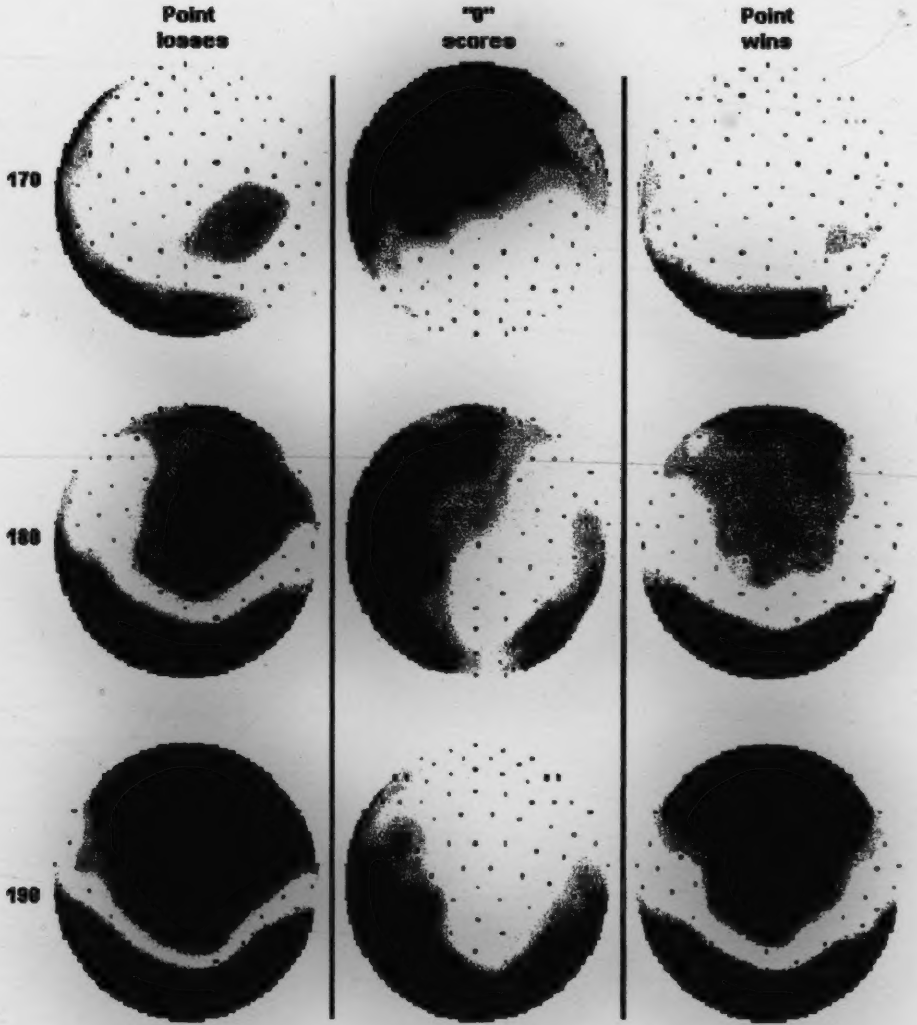

Figure 5.27 Reinforcer responses in the low craving group from 170-190 ms following stimulus presentation. Rows display the average brain activity in 10ms increments over the timespan comprising the P220 response; time slices chosen to best illustrate differences between the reinforcer types, even though the peak amplitude occurs 30ms later. The columns represent, respectively, negative reinforcers (point losses), neutral reinforcers ("0" scores), and positive reinforcers (point wins). Note the relative absence of activity in response to the neutral cue (P220 response in Figure 5.25 *vs.* 5.24 or 5.26). This discrepancy is observed in all groups, but is least pronounced in the high craving group (Figure 5.29).

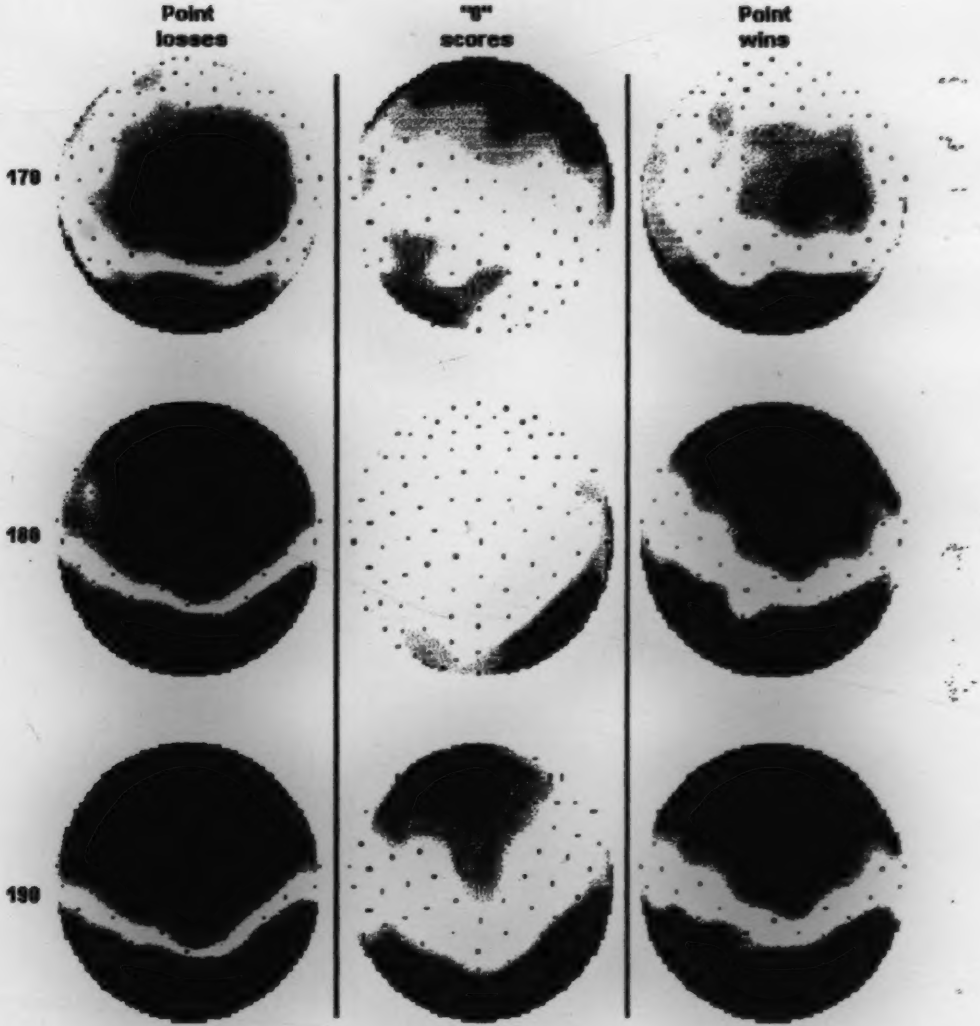

Figure 5.28 Reinforcer responses in the medium craving group from 170-190 ms following stimulus presentation. Displays data in same manner as presented in Figure 5.27.

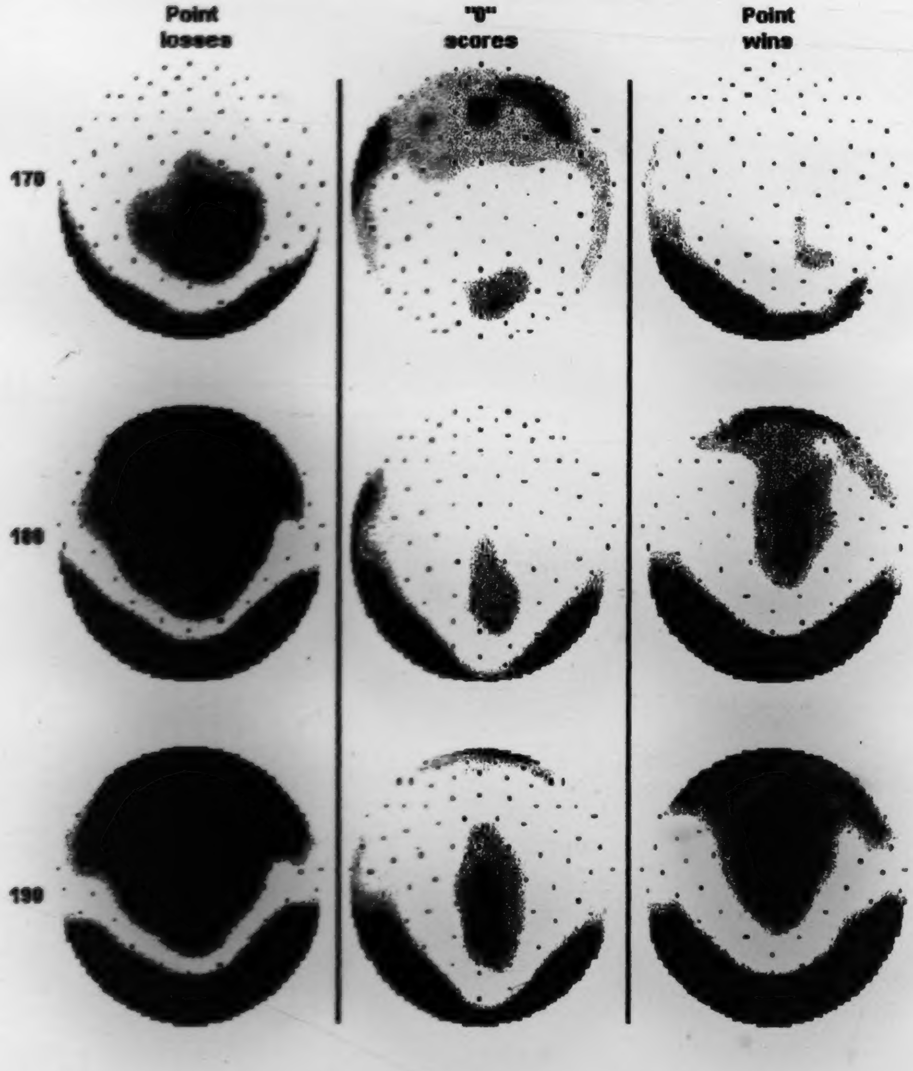

Figure 5.29 Reinforcer responses in the high craving group from 170-190 ms following stimulus presentation. Displays data as presented in Figure 5.27. Note the relatively stronger response to the negative than the positive stimuli for this group of subjects; i.e., responses to positive stimuli appear to be very similar to responses to neutral stimuli.

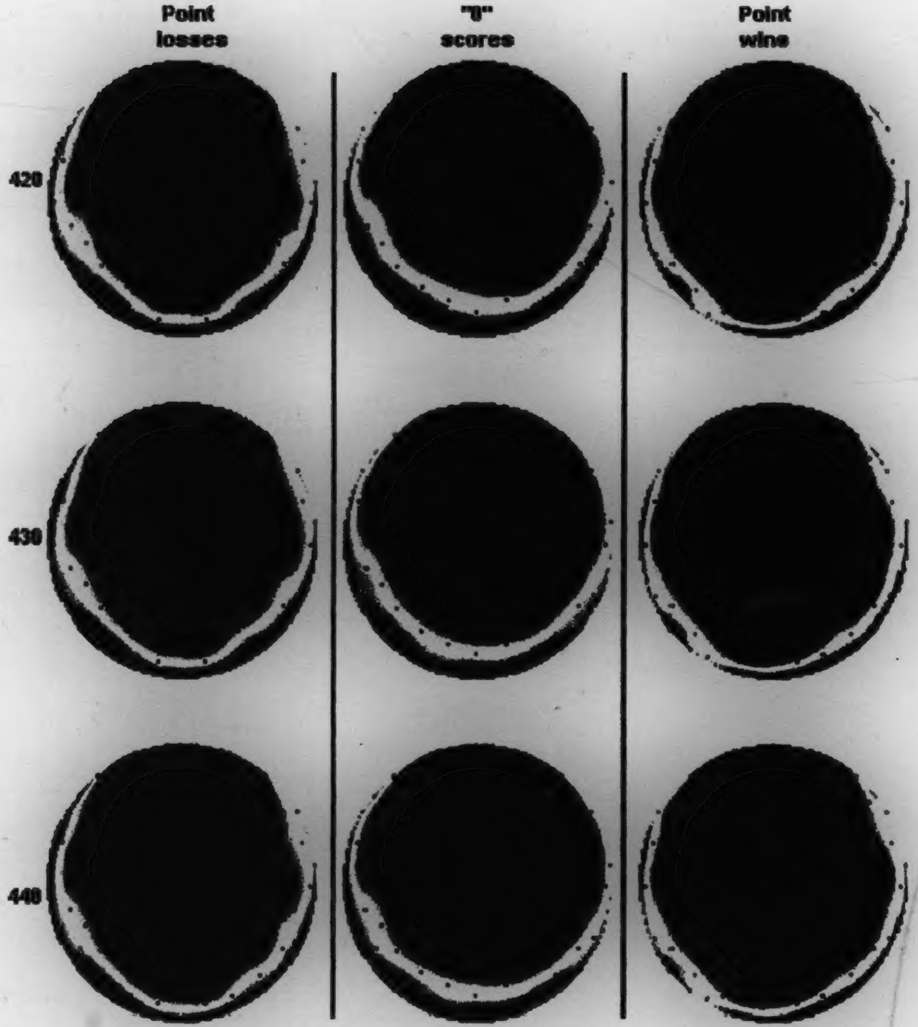

Figure 5.30 Reinforcer responses in the low craving group from 420-440 ms following stimulus presentation. Each column represents time-lapse ERP responses in 10ms increments over the timespan comprising the initiation of the P3b response. The columns represent, respectively, negative reinforcers (point losses), neutral reinforcers ("0" scores), and positive reinforcers (point wins). Few effects were noted for the P3b as a result of craving severity.

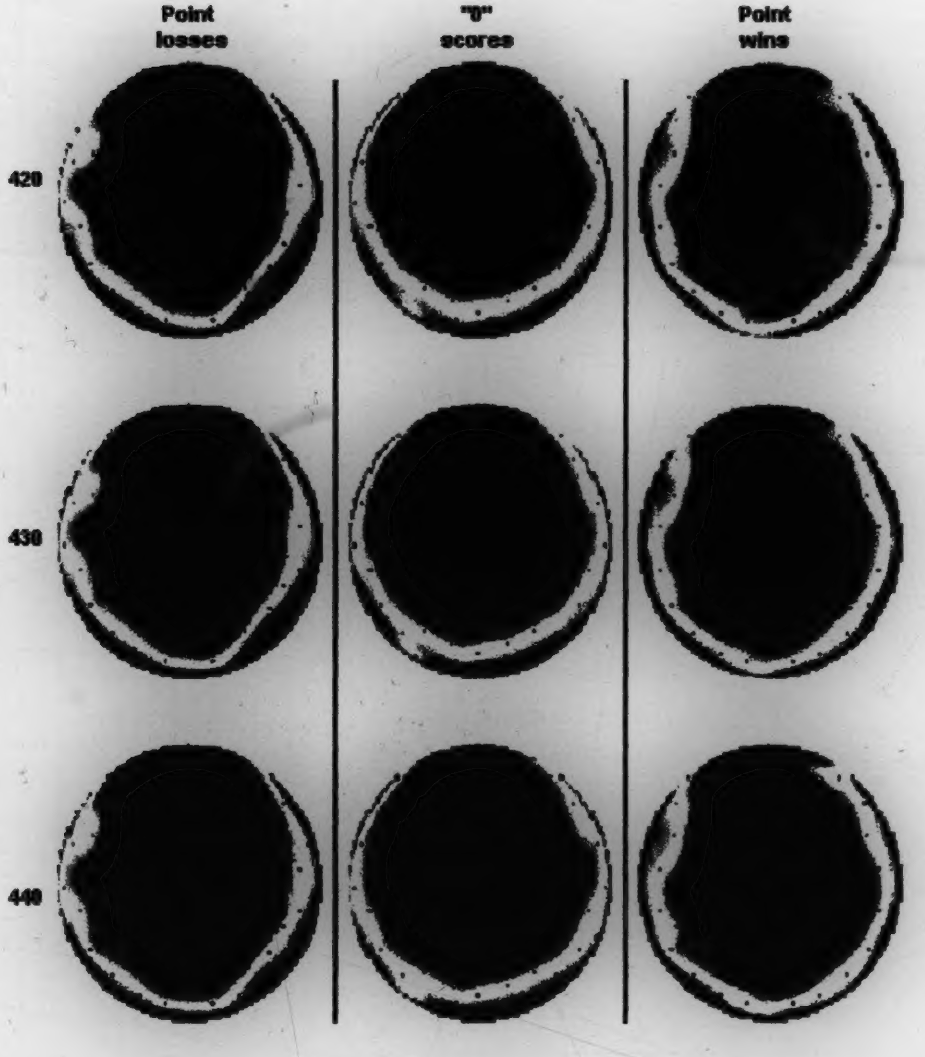
Point losses
"0" scores
Point wins
420
430
440

Figure 5.31 Reinforcer responses in the medium craving group from 420-440 ms following stimulus presentation. Each column represents time-lapse ERP responses in 10ms increments over the timespan comprising the initiation of the P3b response. Displays data as presented in Figure 5.30.

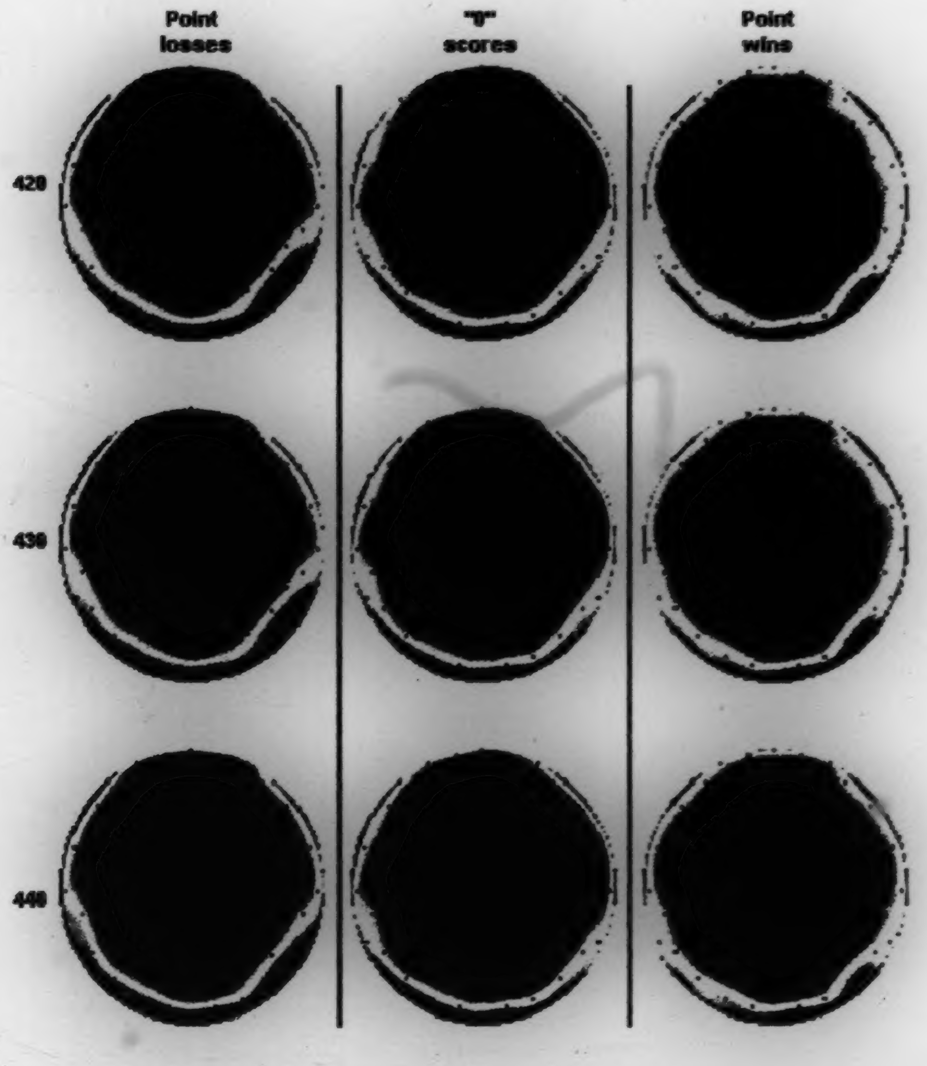
Point losses
"0" scores
Point wins
420
430
440

Figure 5.32 Reinforcer responses in the high craving group from 420-440 ms following stimulus presentation. Each column represents time-lapse ERP responses in 10ms increments over the timespan comprising the initiation of the P3b response. Displays data as presented in Figure 5.30.

Variable	*df*	**Component** **‘P220’**	 **‘P3b’**
7 electrode gps x 3 reinforcer types			
CRAVING	2,42	2.41	1.09
STIM	2,84	**20.56*** **	***6.60****
STIMxCRAVING	4,84	0.54	*1.12*
ELECTRODE	6,252	***29.16*****	***46.09*****
ELECTRODExCRAVING	12,252	*0.60*	*0.40*
STIMxELECTRODE	12,504	***7.16*****	***4.55*****
STIMxELECTRODExCRAVING	24,504	*1.11*	*0.74*
2 sides x 3 reinforcer types			
CRAVING	2,42	2.79†	1.72
SIDE	1,42	0.53	0.08
SIDExCRAVING	2,42	**5.15****	2.50†
VALENCE	2,84	**24.42*****	**4.33***
VALENCExCRAVING	4,84	0.64	1.22
SIDExVALENCE	2,84	0.03	**3.99***
SIDExVALENCExCRAVING	4,84	**2.70***	1.54

†<.10; *<.05; **<.01; ***<.001

Table 5.3 ERP amplitudes in response to reinforcers. Scores are presented as F-values. (Greenhouse-Geisser corrected significance levels italicized)

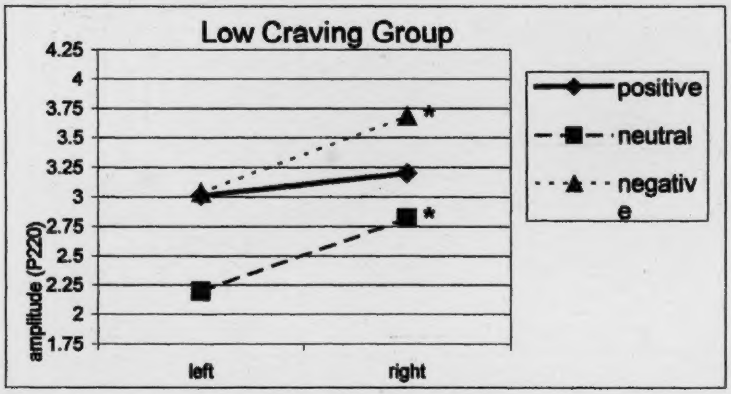

Figure 5.33a Interactions between reinforcer valence and hemisphere in terms of amplitude of the P220 for the low craving group

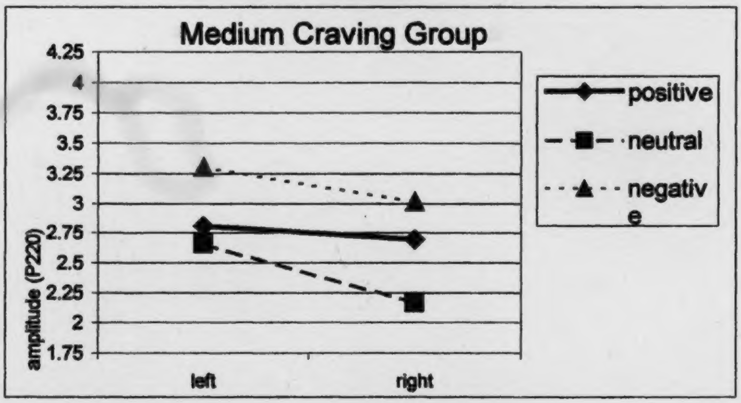

Figure 5.33b Interactions between reinforcer valence and hemisphere in terms of amplitude of the P220 for the medium craving group

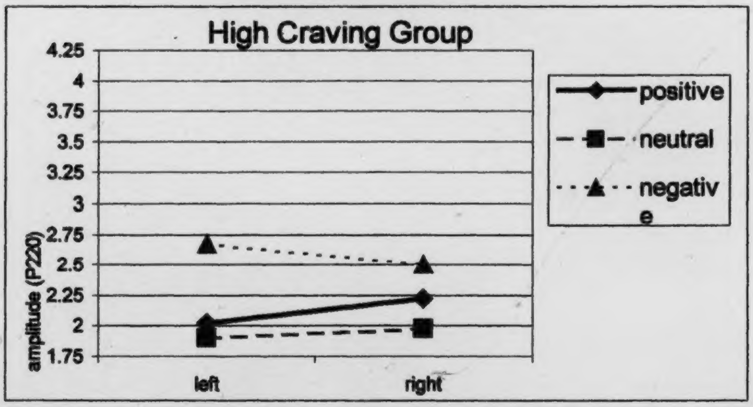

Figure 5.33c Interactions between reinforcer valence and hemisphere in terms of amplitude of the P220 for the high craving group

CHAPTER SIX: NEUROPSYCHOLOGICAL MEASURES

Rationale

If frontal lobe deterioration plays a role in craving, it may help to explain some of the cognitive deficits associated with drug dependence. Neuropsychological tests allow us to measure the extent and nature of cognitive difficulties associated with cravings in a drug dependent population and provide an effective method of verifying the extent of frontal lobe involvement in dependence, as they are sensitive to damage in these regions.

Moreover, an understanding of the exact nature of the deficits associated with dependence is important, as they may play a role in treatment efficacy (Horner, 1999). Clearly, deficits observed in addiction are important because treatment entails, "situations in which new learning is required, new concepts must be assimilated, and information processing and learning strategies are developed" (Wallace, 1986). Furthermore, these impairments may not be obvious in either verbal skills or physical presentation. For a wide-ranging review of the experimental evidence linking prefrontal cortical (PFC) damage in different regions with cognitive and affective deficits, particularly in terms of decision-making, the reader is directed to Krawczyk (2002).

Previous Neuropsychological Investigations of Alcohol and Cocaine Addiction

Given the connectivity of the PFC with the mesocorticolimbic circuitry, frontal lobe deficits are of particular interest in dependence. Dysfunction of the PFC is implicated in some of the personality traits and behavioural abnormalities noted in primary alcoholics (Wiers et al., 1994), yet few associations have been found between abnormal personality profiles and neuropsychological test performance (Rosselli et al., 2001).

The neuropsychological effects of alcohol abuse are relatively well understood, with alcoholics generally showing impairment in "frontal lobe tasks" and tests of visuospatial skills (suggesting right hemispheric involvement; Chelune and Parker, 1981), despite preserved Full Scale and Verbal IQ scores (McCrady and Smith, 1986). Frontal lobe tasks, including indices of abstract thinking, problem solving, and those requiring the ability to profit from feedback, seem related to length of alcohol abuse (Chelune & Parker, 1981). Extent of damage appears to correlate with a broader range of cognitive dysfunction, with Korsakoff patients (who have pervasive damage in the diencephalon, cerebellum, and periaqueductal gray as well as the frontal lobes) demonstrating a spectrum of cognitive deficits (Brand et al., 2003). Alcoholics' problems appear to reflect inefficient use of problem-solving strategies, or difficulties judging when to switch strategies (McCrady and Smith, 1986). As well, they are prone to poor encoding skills in the learning of new information, particularly tasks requiring paired-associative learning (McCrady and Smith, 1986). As mentioned previously, some of the neuropsychological impairments in alcoholics appear to be reversible following abstinence, although this effect appears to be moderated by age (Chelune and Parker, 1981; McCrady and Smith, 1986).

Neuroimaging confirms frontal lobe involvement. A PET study looking at performance of the Wisconsin Card Sorting Test (WCST), a classic test of frontal lobe function, found depressed rates of glucose metabolism in the medial frontal cortex of alcoholics (Adams et al., 1993). While their mean IQ scores were in the average range, the number of concepts attained and error rates evidenced impairment; moreover, degree of atrophy, metabolic functioning in the anterior cingulate gyrus, and WCST scores were significantly correlated. Also using PET, Boller and associates (1995) examined performance on the Stroop task and verbal fluency test in chronic alcoholics. They too found marked hypometabolism in the medial prefrontal and dorsolateral prefrontal cortices, and the former correlated both with verbal fluency and Stroop interference time. Using the same tasks as Boller's group, Dao-Castellana et al. (1998) reported hypometabolism in the mediofrontal and left dorsolateral regions, perhaps secondary to diencephalic lesions.

Fewer accounts of neuropsychological function have been made among stimulant abusers. Horner (1999) provides a review of neuropsychological studies of attention in cocaine abusers. Among the 17 studies he reviews, few deficits are consistently reported, and many have contradictory findings (for instance, 4 studies found impairment on the Trails B subtest, while another 4 did not). Overall, the studies suggested deficits in information processing speed, although results were not always consistent, and some tests (e.g., the Paced Auditory Serial Addition Task) expected to show deficits did not. Other studies appear to implicate right hemisphere processing deficits, with difficulties in tasks with a visuo-spatial component, such as the Rey Figure copy (Rosselli et al., 2001), Arithmetic, and Grooved Pegboard (Smelson et al., 1999). These authors reported that lifetime cocaine use, but not days clean, correlated with test scores, suggesting that decline was a result of long-term use.

However, certain cautions need to be made when examining neuropsychological studies of substance abuse. These include considerations regarding the specific tests chosen; sample size; specific drug of abuse (and other drugs used); amount used and duration; length of abstinence at evaluation (and whether this abstinence was monitored); and comorbidity of other psychiatric illness. For a detailed discussion of these factors, the reader is referred to Horner (1999). Further, it is important to bear in mind that neuropsychological tests measure brain damage, and may not be sensitive to transient state changes, such as cravings.

Neuropsychological Measures Utilized in this Study

Neuropsychological measures included in this study were chosen specifically for their known relation to frontal lobe damage, and their ability to index the processes of expectancy and affect, as relating to reinforcement-based learning. Specifically, some relevant skills subserved by frontal lobe function include generation of flexible responses to changing demands (Tarter and Mezzich, 1992), problem solving (Bonner, 1996), decision making in novel situations (Godefroy and Rousseaux, 1997), self-regulation of behaviour, abstraction, concept formation (Neary, 1995), perseveration, response inhibition, and the ability to engage or disengage attention appropriately when switching tasks (Cummings, 1995). The process of expectancy formation is likely critical to most of these functions. Other frontal lobe skills such as goal persistence and strategic planning of goal-directed behaviour (Tarter and Mezzich, 1992), implicate emotional functioning. The state of being "stimulus bound", which has a high relevance for the electrophysiological task employed, has also been related to frontal lobe deficits (Cooper, 2002). More generally, these tasks index "executive functioning", a set of cognitive processes associated with behavioural planning and modulation (Brand et al., 2003) known to have real-world implications.

All neuropsychological tests and questionnaire measures (see Chapter 7) were administered in the same order to all subjects, except when individual tasks had to be omitted in order to meet time constraints. These tasks are outlined below.

Wisconsin Card Sorting Task. The Wisconsin Card Sorting Task (WCST) requires the subject to develop strategies regarding how to sort cards into piles. All cards can be sorted by colour, number, or form; however only one of the contingencies is in effect at a given time. The subject is not told how to sort the cards, but is told whether each move is "right" or "wrong". Once the subject has successfully sorted 10 cards using one strategy, the contingency is changed without telling the subject. He must then attempt different strategies for sorting the cards, based on feedback alone, until he finds the correct one. Over the course of the task, the subject is required to successfully complete 6 categories (each category twice), or sort the cards until all 128 are completed.

The WCST measures traits of frontal lobe function such as concept formation, perseveration, and set shifting. Quantitative measures include total number of categories achieved (/6), total number of trials, correct trials, number of perseverative and nonperseverative responses, and number of perseverative and nonperseverative errors.

Kephart's Repeating Patterns. In Kephart's Repeating Patterns, the subject is required to complete a series of line drawings. He is presented with a short repetitive pattern, and asked to continue the pattern across the length of a page. Although this is not a speeded or timed task, the subject is encouraged to work relatively quickly. This task requires the individual to maintain set and avoid perseveration. For the purposes of this study, an additional four patterns (developed with neuropsychologist Ivan Kiss in 1996) were added to the standard four typically administered, in order to encourage and examine perseveration and conscientiousness between similar task sets.

Raw number of errors is recorded for each pattern, with one composite score for overall performance. In addition, potentially relevant errors, such as changes in size (e.g., micrographia), inappropriate spacing, and pattern misperceptions were also scored. However, it should be noted that the scoring on this task is somewhat subjective.

Trails A and B. Trail A is a connect-the-dots type of task, in which the subject must draw a continuous line from number 1 to 25 as quickly as he can. Trail A is administered to act as a "speed control" for Trail B. Trail B is an equivalent task, however, the subject must alternate between numbers and letters (e.g., 1-A-2-B-3-C, etc.), thus adding a cognitive processing component to the task. The tasks are timed, and both times and raw number of errors are recorded. A measure of "switching time" is computed by subtracting the time for Trail A from that of Trail B. Both trials are preceded by short sample tasks.

Trail B is of interest, as it requires the individual to constantly shift set (between letters and numbers). As such, it reveals such frontal lobe traits as perseveration (when the individual attempts to use numbers or letters alone) and difficulty changing set.

Sequential Movements. In Sequential Movements, the subject is asked to repeat a series of manual hand gestures, which increases from 1 to 4 discrete movements in a row. Each individual set is demonstrated to and repeated by the subject 3 times; then, the set is presented a final time and the subject is required to perform 5 repetitions unaided. Right and left hands are scored separately. The number of correct trials for both the demonstration (/3) and repetition (/5) portions are recorded. Additionally, any perseverations (i.e., additional unrequested trials after the 5 repetitions) were noted and tallied.

This task reveals aspects of working memory, inability to shift set, as well as perseveration, since the subject must monitor himself to stop at five repetitions.

Controlled Word Association Task (COWA). The subject is asked to generate as many words as possible beginning with a given letter (F, A, or S) in a 60 second period. Semantic categories (e.g., Animals; Foods) were not administered due to time constraints. Cognitive speed (by a count of words generated every 15 seconds, whether allowable or not), perseveration (repetitions of the same word), and intrusions (non-words, disallowed words [names and numbers], or incorrect letter words) were measured.

Cognitive Estimation Task. Individuals are verbally given a list of questions, and asked to make an estimation of the correct response (e.g., "How many slices are there in a sliced loaf?"). A subset of ten items thought to have maximum discriminative capacity was chosen based on consultation with neuropsychologist Gail Matazow (personal communication, February 1, 2000). The full set of questions from which the subset was chosen is presented in Kopera-Frye et al. (1996). Because these authors found wider response ranges in patients than controls, and because our study did not employ controls, this test was scored by calculating z-scores based on group performance for the individual items, with subsequent calculation of each individual's mean z-score.

For this study, it was speculated that the ability to generate expectations may be reflected in difficulties in terms of developing reasonable estimates in everyday life.

Proverb Interpretation. In the Proverb Interpretation task (Gorham, 1956), the individual is presented with a list of 12 proverbs and asked to provide their correct interpretations. Do to difficulties in reading the handwriting of a number of the subjects, and the ostensibly low effort observed on the task (e.g., a number of subjects provided one-word "synonyms" for each phrase, and 7 participants (14%) attempted fewer than half the items), and the fact that it was the task most often excluded given time constraints, scoring was comprised of tallying the raw number of attempted items.

Results

Correlational Analysis: Individual Test Scores

A preliminary analysis (not shown) examined correlations between individual scores and the MMCQ; however, this approach yielded a very large number of correlations, and so was prone to a high rate of Type I error. However, due to the excessive number of observations, Bonferroni correction was not considered a good alternative, due to inflation of Type II error. Means and standard deviations for the neuropsychological measures are presented in Table 6.1 for each of the three craving groups.

One observation, however, bears discussion before proceeding. As noted with the behavioural results on the gambling task discussed in the previous chapter, craving was significantly correlated ($r = .314$, $p < 0.05$; see Figure 6.1) with increased number of words generated on during the verbal fluency task (COWA), but only during the first half of each trial (second half $r = .146$, $p > .3$). Furthermore, a comparison of mean scores between the weak and severe craving groups on several measures *generally* found faster performance in the latter group. For instance, the severe craving group generated an average of 9 extra words during the COWA, and completed both the Trail A and B subtests faster, on average. These non-significant differences are suggestive. Rodriguez Holguin and co-workers (1999) also report a trend toward faster response times and better performance in an oddball target detection task among abstinent alcoholics than normal controls. Similarly, better performance among cocaine abusers than controls has been observed on the WCST (Hoff et al., 1999; as cited in Grant et al., 2000). Increased false alarm rates were also noted in this group, suggesting that the improved performance was associated with increases in impulsive responding.

Principal Components Factor Analysis

In order to reduce the number of variables, and to judge whether conceptually important relationships, such as lateralization, perseveration, or impulsive responding, could be extracted from the test scores, a principal components factor analysis (PCA) was performed on the neuropsychological measures. Factors were rotated using varimax rotation with listwise deletion of missing values. The total *n* obtained for the analysis was 45.

10 factors emerged with eigenvalues greater than 1.0, with a cumulative explained variance of 80.8%. For the most part, these tended to reflect multiple measures of separate tests (although see MANOVA, next section), and so we will forego a detailed discussion of putative conceptual factor meanings. The 10 factors are presented in Table 6.2.

Correlational Analysis: Factor Scores

Correlations between the factor scores and the subscales of the MMCQ are presented in Table 6.3. While a couple of correlations (factors 6 and 10) were each significant with one of the subtests at the .05 level, none met the criteria for significance given Bonferroni correction (.05/10 - .005), nor a slightly more stringent probability level of .01. Since neither of these factors correlated with the total score or any other subtest, the observed correlated are likely not meaningful.

Multivariate Analysis of Variance

An initial multivariate analysis of variance (MANOVA) of all ten factors was found to be only marginally significant ($p < .08$). However, an examination of the ten factors suggested that factors 3 and 4 might directly index hemispheric function, and so were of substantive theoretical interest. These two factors were chosen for inclusion into another MANOVA. Examination of quantile plots (Morrison, 1990) indicated that both factors were normally distributed and free from outliers.

Roy's Greatest Characteristic Root criterion indicated a significant difference between the groups ($F_{2,42} = 3.92$; $p < .05$). Simple contrasts were performed, and Roy-Bose simultaneous 95% confidence intervals (CIs), which control overall Type I error, were applied in order to evaluate the pattern of the differences among the means. Only CIs between the low and moderate craving groups for factor 3 (right-sided deficits; i.e., LH function) indicated a significant difference [95% CI = .073, 1.836]; groups 2 and 3 did not differ from one another [95% CI = -1.454, 0.310]. Significant contrasts were not found for either comparison on factor four [low vs. moderate 95% CI = -.992, 0.832; moderate vs. severe 95% CI = -.295, 1.528].

Both factor scores were then entered together into a discriminant analysis, in order to estimate their relative contributions to the main effect. The discriminant analysis generated two functions, both of which were significant. The Wilks' Lambda score for the first function yielded a χ^2 value of 11.44 ($p < .05$), while the second function had a χ^2 value of 4.33, ($p <$ .05). The standardized discriminant function coefficients are presented in Table 6.4, with the associated structure matrix presented in Table 6.5a. The means of the discriminant functions for all 3 craving levels are presented in Figure 6.2.

As presented in Table 6.5b, the overall classification rate using the 2 discriminant functions was 55.6%, as compared to the three-group chance classification rate of 33.3%. The discriminant function analysis was relatively better at classifying individuals in the moderate and severe craving groups (60% correct classification each), than the low craving group (46.7% correct classifications, with misclassifications divided evenly between the other two groups).

While these factor scores, which load mostly on lateralized performance scores in sequential movements, are thought to reflect dysfunction of the frontal regions, this cannot be conclusively demonstrated in this study. However, there is indirect evidence supporting this contention. Grafman and colleagues (1986) showed that individuals with left or bilateral orbitofrontal lesions were less likely to complete 6 categories in the WCST than those with right orbitofrontal lesions or controls; we found that sequential movements total scores on the right hand (LH) predicted the number of categories individuals would complete in the WCST ($\chi^2_{(65)} = 98.43$, $p < .005$), while scores on the left hand did not ($\chi^2_{(70)} = 78.00$, $p > .2$).

Discussion

Our finding of few correlations between neuropsychological test performance and craving was somewhat surprising, but in line with previous studies showing no difference between risk groups (alcoholic males, their nonalcoholic brothers, and matched controls), in performance on the Halstead-Reitan Category Test, a well-known test of executive functioning (Hill et al., 1995). Previous investigations have also failed to find a relationship between neuropsychological test scores and CT scan abnormalities in abstinent alcoholics (Marchesi et al., 1997), and between neuropsychological scores and evoked potentials (Ciesielski et al., 1985). These results are also suggestive in light of findings of Bechara and colleagues (2001), who showed that performance on the gambling task could not be predicted by performance on standard executive function/frontal lobe tasks, including the WCST, Stroop, or Tower of Hanoi. Similarly, Tranel and co-workers (2002) found preserved performance on the WCST, Controlled Word Association, and Trail Making Tasks, in the presence of performance decrements on the gambling task, in individuals with ventromedial PFC damage. Further, these authors found no systematic differences between individuals with LH or RH damage. Grant and co-workers (2000) also found differences in performance by drug abusers on the gambling task, but none in the WCST. These results suggest that damage associated with impairment in reinforcement-based learning is not readily explained as a function of simple cognitive deficits (Tranel et al., 2002).

This lack of correlation may stem from several causes. It may be in part because the most characteristic deficits of frontal lobe damage (as tested using neuropsychological instruments) are induced by dorsolateral, rather then ventromedial prefrontal damage (Bechara et al., 2001; Fuster, 2001; Grafman et al., 1986; Grant et al., 2000; see Krawczyk, 2002 for a review); dorsolateral damage appears to be related to working memory cognition, rather than decision-making *per se* (Rogers et al., 1999, but see Adinoff et al., 2003). In fact, as Cummings (1995) notes, "few neuropsychological deficits occur in patients with medial frontal lobe lesions". It has also been argued that some patients with physiological impairment may attempt to compensate by increasing the effort expended in order to maintain "normal" performance for limited periods (Polo et al., 2003). Thus, while individuals may perform normally on neuropsychological tasks, their impairment is clear in terms of their everyday functioning. Our lack of findings may also reflect the reported wide range of neuropsychological impairment often found in alcoholics, even within well-matched groups (Chelune and Parker, 1981).

Conversely, it may be that there is simply limited correlation between frontal lobe damage, as reflected by neuropsychological functioning, and phasic state changes such as craving. As Cepeda-Benito and Tiffany (1996) note, "it is possible that the strongest evidence of associations between craving report and [other measures] may only emerge when these variables are *assessed concurrently*" (Cepeda-Benito and Tiffany, 1996, italics added). That is, alterations in cognition correlated with craving may be not be measurable when the subject is not acutely craving.

A few noteworthy relationships were, however, observed. For instance, we found increased verbal output on the Controlled Word Association Task during the first half of the subject's allotted time. Increased verbal output may be indicative of LH hyperactivity. In support, Molina and Pelham (2001) reported that, among children with ADHD, better verbal comprehension was related to increased smoking behaviours, while higher IQ scores (which load heavily on verbal skills; Sattler, 1992) were related to earlier ages of trying a drink and increased use of cigarettes at follow-up. As discussed previously, this finding is in agreement with that of increased behavioural output in the first block of the gambling task (see Chapter 5). Closer examination also found faster speeds in the high craving group for other measures, although these were not significant. Taken together, these findings are suggestive of enhanced responsiveness to novelty, or behavioural activation more generally. Hence, Ciesielski and co-workers (1985) may be correct when they note that, "neuropsychological assessment of cognitive deficits in chronic alcoholics is a limited measure that *relies exclusively on behaviour*" (Ciesielski et al., 1985, italics added).

Finally, a MANOVA found that the scores of two rotated factor components, which appeared to represent RH and LH function, were able to discriminate level of craving, as predicted by our model. Previous investigations (e.g., Schaeffer and Parsons, 1986) have found simple tests of lateralization (grooved pegboard non-dominant hand score) to discriminate between alcoholics and normal social drinking controls.

Summary

In order to validate the role of the prefrontal cortical systems in craving and dependence, we administered a number of neuropsychological measures thought to index frontal lobe executive function. Generally, few significant effects were found. However, a MANOVA did lend support to the model suggesting abnormal lateralization associated with craving. In addition, increased responding on the first half of the Controlled Word Association Task supported the notion of increased behavioural activation in response to novelty being associated with craving severity.

	Low Cravings	**Moderate Cravings**	**Severe Cravings**
Controlled Word Association			
Total acceptable	34.27 (11.76)	32.53 (14.28)	41.53 (10.83)
Total words generated	36.93 (13.01)	35.93 (15.05)	46.00 (14.52)
Proportion acceptable of total	.93 (.04)	.90 (.08)	.91 (.06)
Perseverations	1.07 (1.16)	1.80 (2.70)	1.47 (1.51)
Unacceptable words	1.60 (1.12)	1.60 (1.50)	3.00 (3.80)
Sequential Movements			
Total score - right hand	15.00 (3.82)	18.40 (3.60)	16.60 (3.02)
Total score - left hand	16.67 (5.45)	18.20 (4.38)	20.20 (2.24)
Total score - right minus left	-1.67 (4.65)	.20 (4.80)	-3.60 (3.74)
Perseverations - right hand	1.53 (1.25)	1.67 (2.26)	1.27 (1.22)
Perseverations - left hand	1.67 (1.45)	1.13 (1.13)	1.33 (.98)
Perseverations - right minus left	-.13 (1.06)	.53 (2.07)	-.07 (1.53)
Trail Making Test			
Trails A (total time, seconds)	26.67 (7.07)	25.00 (7.55)	20.87 (6.23)
Trails A (errors)	.73 (.59)	.67 (.82)	.33 (.49)
Trails B (total time, seconds)	76.53 (18.83)	69.53 (24.88)	60.73 (20.03)
Trails B (errors)	.93 (.80)	.53 (.83)	.53 (.52)
Switching time	49.87 (14.58)	44.53 (22.54)	39.87 (16.56)
Proverbs			
Attempted	8.87 (2.53)	9.80 (2.37)	9.33 (2.26)
Kephart's Repeating Patterns			
Mean total produced	25.43 (4.07)	24.85 (4.20)	25.93 (3.33)
Mean errors	2.42 (1.07)	2.76 (2.34)	2.30 (1.13)
Probability - adding extra space	.06 (.15)	.03 (.05)	.03 (.07)
Probability - misperception of pattern	.13 (.15)	.17 (.21)	.12 (.11)
Probability - incorrectly alternating size/shape	.16 (.14)	.05 (.09)	.11 (.11)
Probability - micro/macrographia	.15 (.16)	.12 (.15)	.07 (.09)
Cognitive Estimation			
Mean z-score, compared to group	-.09 (.37)	.19 (.34)	-.08 (.34)
Wisconsin Card Sorting Task			
Correct responses	73.87 (11.73)	75.00 (7.18)	77.07 (11.21)
Perseverative responses	21.80 (18.89)	13.53 (7.66)	19.40 (13.89)
Perseverative errors	19.13 (15.97)	12.27 (6.91)	17.13 (11.51)
Non-perseverative errors	14.87 (8.72)	12.67 (9.70)	14.73 (8.65)
Categories	4.60 (1.80)	5.27 (1.33)	4.87 (1.36)

Table 6.1 Neuropsychological test results in the weak, moderate, and severe craving groups; all scores presented mean (SD). Note, redundant scores were not entered into the principal components factor analysis, and constituent (rather than summed) scores were used where applicable.

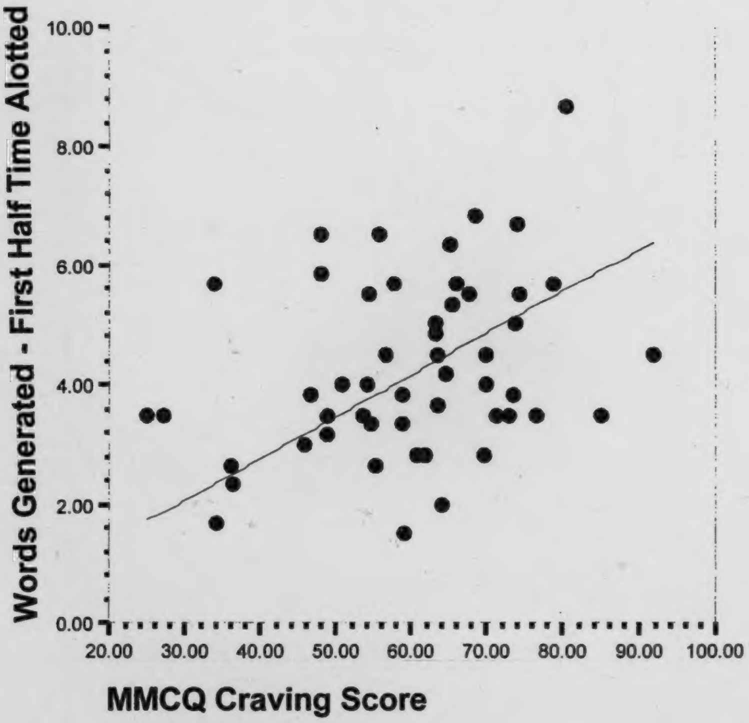

Figure 6.1 Correlation between craving and words generated in first half of allotted time: Controlled Word Association Task.

Factor	Component Measures	Eigenvalue	Total %Variance Explained	Cumulative Total % Variance	Items
1	WCST - errors (4 items)	5.13	18.31	18.31	4
2	COWA performance (4 items)	3.34	11.93	30.24	4
3	Sequential movements - right side deficits (3 items); Cognitive estimation (1 item)	2.64	9.44	39.68	3
4	Sequential movements - left side deficits (3 items)	2.50	8.94	48.63	3
5	Kephart's repeating figures - errors (2 items)	2.21	7.90	56.53	2
6	Trails A/B - errors (2 items); Sequential movements perseverations (1 item); Proverbs - trials attempted (1 item)	1.91	6.81	63.34	4
7	Trails A/B - times (2 items)	1.44	5.13	68.47	2
8	WCST - correct trials (1 item); Kephart's repeating figures - errors (1 item)	1.27	4.54	73.01	2
9	Sequential movements - left side perseverations (1 item); Kephart's repeating figures - total produced (1 item)	1.12	4.01	77.02	2
10	Kephart's repeating figures - errors (2 items)	1.07	3.82	80.84	2

Table 6.2 Principal components analysis of the neuropsychological test scores (Listwise *n* = 45)

Factor	MMCQ Total Score	General Descriptive Information	Behaviour Subscale	Cognition Subscale	Emotion Subscale
1	.092	.224	.069	.164	.036
2	.232	.098	.205	.149	.276†
3	.070	-.078	.074	.032	.083
4	.182	.008	.169	.164	.172
5	.086	-.088	.052	.060	.120
6	-.239	.189	-.186	-.124	**-.332***
7	.021	-.093	-.041	.047	.054
8	-.079	-.135	-.140	-.047	-.032
9	-.043	.019	-.073	-.034	-.014
10	-.228	-.186	**-.300***	-.228	-.116

†Correlation marginally significant (.05 < p < .09)
*Correlation is significant at the 0.05 level

Table 6.3 Correlations between MMCQ craving scores and factor scores derived from the neuropsychological test variables.

Standardized Canonical Discriminant Function Coefficients

	Function	
	1	2
Factor 3	1.000	.017
Factor 4	-.018	1.000

Table 6.4 Standardized discriminant function coefficients of MMCQ factors 3 and 4 (behavioural asymmetries).

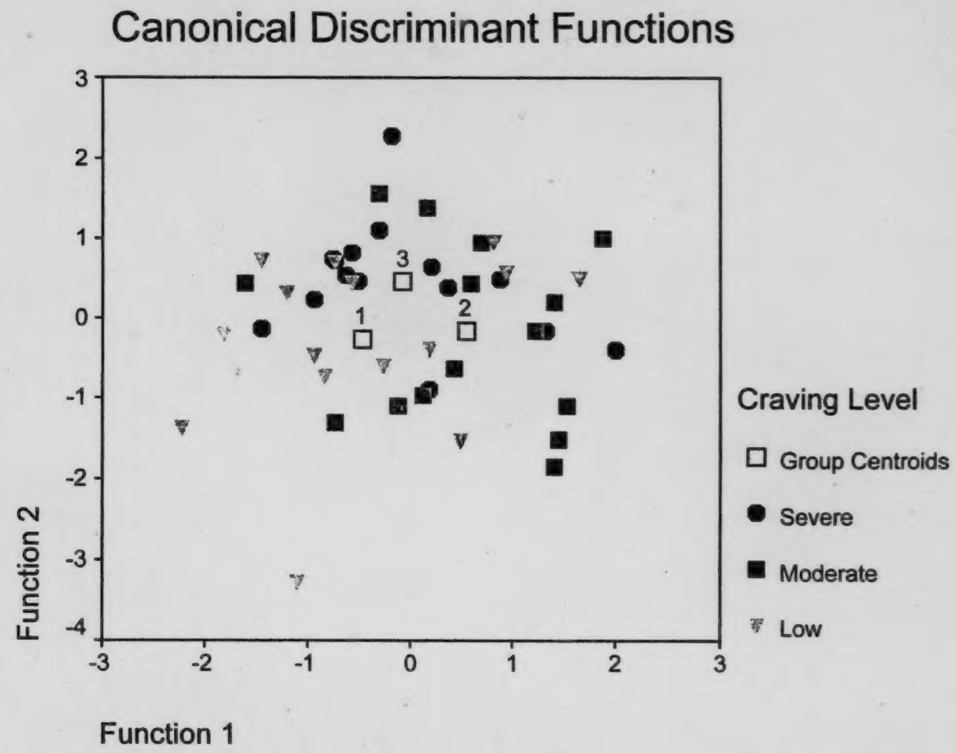

Figure 6.2 Canonical discriminant functions of neuropsychological test scores related to functional asymmetries and level of craving

Structure Matrix

	Function	
	1	2
factor 3	1.000*	.018
factor 4	-.017	1.000*

Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions
Variables ordered by absolute size of correlation within function.

*. Largest absolute correlation between each variable and any discriminant function

Table 6.5a Structure matrix of neuropsychological test factor scores 3 and 4, which index lateralization.

Classification Results

			Predicted Group Membership			
		Craving Group	Low	Moderate	Severe	Total
Original	Count	Low	7	4	4	15
		Moderate	3	9	3	15
		Severe	2	4	9	15
	Percentage	Low	46.7	26.7	26.7	100.0
		Moderate	20.0	60.0	20.0	100.0
		Severe	13.3	26.7	60.0	100.0

a. 55.6% of original grouped cases correctly classified.

Table 6.5b Classification results using neuropsychological test factor scores 3 and 4, which index lateralization. Note the relatively better classification results for the moderate and severe craving groups.

CHAPTER SEVEN: QUESTIONNAIRE MEASURES OF AFFECT

Rationale

Questionnaire measures were employed because they provide brief and unobtrusive methods of measuring affective and personality traits characteristic of substance dependence. They also have the advantage of requiring little interaction with the subject, thereby reducing demand effects. Further, their reliability and validity are typically well established.

Since negative affect is a commonly noted characteristic of substance dependence, several measures of mood and personality that might indicate heightened negative affect, including depression and anxiety, were administered. Additionally, because sensation seeking is reliably associated with substance abuse, it was also assessed.

Questionnaire Measures Utilized in this Study

Criteria for Substance Dependence. A checklist of the 7 *DSM-IV* criteria (see Chapter 1, Table 1.2), in a yes/no format, was verbally administered to each subject, to ensure he met diagnostic criteria for dependence. Each subject was thus assigned a dependence score from 0-7.

Problem Use. The Problem Use Scale was based on an adaptation of Curran et al.'s (1997) Problem Alcohol Scale, altered so that questions could apply to drugs other than ethanol (i.e., cocaine). The scale assesses many aspects of drug/alcohol use suggestive of dependence, including behavioural and interpersonal problems, medicolegal consequences associated with excessive use, and a number of affective symptoms characteristic of psychological dependence. Individuals were given the list of 36 questions, and asked how often within the last three years those events/feelings had occurred.

The response scale varies from ‘never’ to ‘6 or more times’, on a scale of 0-3. While the scale used is not ideal (e.g., a score of 2 indicates 3-5 occurrences), subjects were given a detailed account of the response requirements, and were monitored while they completed the first few questions to ensure they experienced no difficulties.

Handedness. The Annett (1970) and Chapman and Chapman (1987) measures of hand preference generate scores of strong, inconsistent, or mixed handedness. There is some overlap between questions on the two scales, and they generally show relatively strong agreement (in this sample, $r = .842$; $p < .001$). The Annett also asks questions regarding handedness of first-degree relatives, and attempts (by primary school teachers, parents, etc.) to change the handedness of the participant. These questionnaires were verbally administered.

Depression. The Beck Depression Inventory, 2nd edition (BDI-II; Beck et al., 1996) is a brief scale comprised of 21 questions, measuring several symptoms of depression, including dysphoria, anhedonia, agitation, fatigue and sleeplessness, changes in appetite, problems with concentration, and anergia. Questions are scored from 0 to 3 points. The subject chooses one statement in each group that best describes the way he has been feeling during the last two weeks; if more than one response is chosen, only the higher score is counted.

Scores obtained classify individuals as minimally, mildly, moderately, or severely depressed. The test shows good reliability (α’s > .90, among English-speaking populations, depending upon group surveyed) with good criterion validity (Smith and Erford, 2001).

Anxiety. The Spielberger State/Trait Anxiety Index (Spielberger et al., 1970) is composed of 40 items, some reverse-scored, on a scale of 1 to 4 points. The index consists of two short forms, assessing general (Trait), and present (State) feelings of tension and anxiety.

For the purposes of this experiment, only the Trait short form was given. Instructions were modified slightly, in that individuals were to report how they felt in the last two weeks (rather than "generally"), in order to make responses more comparable with the BDI-II.

Impulsivity. The Impulsivity subscale of the Basic Personality Inventory (BPI; Jackson, 1996) consists of questions assessing 12 psychological domains. In the BPI, questions are presented from the domains in a pseudorandom fashion, with true- and false-keyed questions alternating within a domain. Due to the amount of material being administered for this study, only the Impulsivity subset of questions was given, and questions were randomized. Two versions were administered, to minimize any order effects.

The Impulsivity subscale consists of 20 true/false questions surveying aspects of impulsivity such as risk-taking, carelessness, and manic behaviour. The BPI manual (Jackson, 1996) describes low-scorers as even-tempered and level-headed, who carefully consider the future before acting, and generally have the patience to cope with lengthy and tedious tasks, while high-scorers lack the ability to think beyond the present or consider the consequences of their actions, are prone to risky and reckless or irresponsible behaviour, and find routine tasks boring. Also according to the manual, drug abusers rate significantly higher than normal controls on this subscale, but alcoholics do not. However, these results were generated in the context of administration of the entire inventory.

Again, subjects were asked to rate themselves and their behaviour based on the preceding two weeks, to increase comparability with the other questionnaire measures.

Sensation Seeking. Developed originally in 1964 by Zuckerman, Kolin, Price and Zoob, the Sensation Seeking Scale V (SSS-V; Zuckerman, 1979) is designed to measure 4 orthogonal domains of sensation seeking. These have been described (Zuckerman, 1990) as: Experience Seeking - the desire to seek new experiences and sensations through lifestyle and travel; Boredom Susceptibility - an aversion for unstimulating or unchanging environments;

Disinhibition - seeking of sensations via social means; and Thrill and Adventure Seeking - a desire to take part in risky physical activities with unusual or uncertain sensory components.

The SSS-V consists of 40 total questions worth 1 point, of which 10 measure each domain. For each item, individuals must choose between two descriptors in a forced choice format, as to which better describes their likes or feelings (e.g., "I get bored seeing the same old faces" *vs.* "I like the comfortable familiarity of everyday friends"). The sensation seeking response receives one point while the alternate response receives 0 points.

Results

All subjects met or exceeded *DSM-IV* criteria for substance dependence (mean = 5.98/7.00, SD = 0.97).

Pearson correlation coefficients were computed in order to examine the relationship between the 7 mood measures (including the sensation seeking subscales as independent measures) and craving. Consideration was given to the problem of Type I error by setting more stringent criteria for significance. While a Bonferroni correction would call for p values to fall below .00625 (.05/8 measures), it was decided that this criterion undesirably increased the odds of Type II error[17] (J. Lind, personal communication, July 11, 2003), particularly considering the fact that 4 of the measures (i.e., the sensation seeking subscales) are related theoretically. As a compromise, we adopted a criterion of $p < .01$.

Correlations between Mood and Drug of Choice

Since one of the topics debated regarding the nature of cravings is the association of personality or mood characteristics determining drug of choice, we investigated this measure by examining the relationship between mood/personality variables and primary drug choice.

Independent t-tests revealed no significant relationships between scores on any of these variables (all p's > .10; Table 7.1).

Correlations Between Craving and Mood

Strong correlations were seen between craving and indices of mood and personality, particularly anxiety. Trends (.01 > p < .05) were evident for both impulsivity and the Disinhibition and Experience Seeking subscales of the Sensation Seeking Scale, as well as for the sensation seeking total score (Table 7.2).

Principal Components Analysis of Craving and Mood Measures

The above results are at odds with those of Mezinskis and co-workers (1998), who found that craving and negative affect loaded onto two relatively separable factors. Therefore, a principal components analysis with varimax rotation was performed to examine the pattern of correlations between the mood and craving variables. Pairwise deletion did not result in any problems with matrix calculations, and was therefore employed. This resulted in *n*'s varying from 45 to 51. Only the Total Score for the MMCQ was included as part of the PCA. This was decided *a priori*, as this score is very highly correlated with its constituent subtest scores (see Chapter 4), is the most normally distributed, and would otherwise be highly overrepresented among the variables entered into the equation, particularly in comparison to Mezinskis et al. (1998), who used only 2 craving measures and 8 mood variables.

The eight original variables separated into three factors, as illustrated in Table 7.3. These three factors accounted for 72.5% of the total variance. Most significantly, the first variable was comprised of anxiety, depression, and craving, with factor loadings between .682 - .918, accounting for 40.0% of the total variance of the items. This verifies that craving does share common variance with negative affect.

The pattern of variance among the other factors is also noteworthy. The second factor, comprised of Thrill Seeking and Experience Seeking appears to index novelty seeking, and may represent an index of DA activity; in our model, this would be associated with cravings during active use/early withdrawal. Likewise, the third factor, comprised of Boredom Tolerance, Disinhibition, and impulsivity appears to index impulsive behaviour, and so may represent 5-HT activity; in our model, this would reflect cravings during abstinence. However, correlations between these factor scores and number of days abstinent did not support this hypothesis (p’s $> .3$ for both factor 2 and factor 3).

Discussion

In the interest of examining the self-medication model and adaptive models of craving (see Chapter 1), we examined the relationship between the various mood/personality variables and the individual’s drug of choice. No relationships were found. In general, these results argue against either of these theories. However, the individuals surveyed had undergone two weeks of inpatient treatment and many were likely still in withdrawal. Nonetheless, the results argue more strongly for the common substrate theory. The findings also lend support to our decision to collapse the alcohol and cocaine groups for analysis.

A number of correlations were observed between craving and mood/personality characteristics. The highest correlations were noted in measures of anxiety, with marginally lower correlations to depression; similar patterns have been observed in alcoholic *vs.* control comparisons (Errico et al., 1993). Our model predicts that craving and coping-related anxiety are related as a result of activation of the left hemisphere.

Of note, the highest correlations of craving with Sensation Seeking were found on the Disinhibition and, to a lesser degree, Experience Seeking subscales. Relationships have been noted between these scales, which are respectively thought to reflect poor impulse control and novelty seeking, and measures of 5-HT and DA (Netter et al., 1996).

Our principal components factor analysis results did not replicate those of Mezinskis et al. (1998), in terms of generating separate craving and mood factors. Several differences between the two studies could help account for this discrepancy. First, the variables used in this study were more complex composite variables, whereas the Mezinskis study employed point values between 0 and 4 for each item. In particular, our craving variable was far more complex, as the Mezinskis study probed only the intensity and frequency of craving. Second, the instrument used in the Mezinskis study asked about feelings "during the past few hours", whereas the current study recorded individuals moods for the preceding two-weeks. Several authors (e.g., Anton and Drobes 1998; Kouimtsidis, 2000) have concluded that scales which are more global or ask users to average their urges over longer periods of time may offer a more reliable measurement. Finally, while the Mezinskis study did index negative affect and impulsive behaviour, there were no questions regarding excitability/novelty seeking. While there is no way to choose between the two sets of findings, the separation of variables into what appear to be DAergic and 5-HTergic mechanisms (in terms of SSS subscale scores) in our factor analysis is certainly noteworthy. Importantly, our results provide general empirical support for the biopsychological model of craving presented in Chapter 3.

Summary

Questionnaire measures of depression, anxiety, and sensation seeking were administered. No relationships were found between the mood/personality variables and drug of choice, so data were pooled. Strong correlations were noted with most measures used, particularly anxiety. These results indicate that negative affect and craving are strongly related. A factor analysis of these measures found a negative affect/craving factor, a sensation seeking factor, and an impulsivity factor. The latter two may reflect DAergic and 5-HTergic mechanisms, respectively. These results provide stronger support for a biological, rather than a psychosocial, model of the role of mood and personality in drug craving.

Measure	Total *n*	Group Mean	Alcohol	Cocaine	*t*-score
Mood					
Depression (BDI)	51	15.10 (9.94)	13.50 (5.64)	16.76 (12.93)	-1.16
Anxiety (STAI)	51	46.94 (9.84)	46.15 (7.35)	47.76 (12.00)	-.57
Personality					
Impulsivity (BPI)	51	10.02 (4.60)	9.58 (4.65)	10.48 (4.60)	-.70
Disinhibition (SSS)	45	5.31 (2.20)	5.29 (2.48)	5.33 (1.91)	-.06
Boredom tolerance (SSS)	47	3.23 (1.77)	3.25 (1.96)	3.22 (1.59)	.06
Thrill/Adventure seeking (SSS)	47	7.89 (2.06)	7.42 (2.21)	8.39 (1.80)	-1.65
Experience seeking (SSS)	47	5.91 (1.79)	5.75 (1.94)	6.09 (1.65)	-.64
Sensation seeking - total score (SSS)	45	22.53 (5.39)	21.71 (6.52)	23.48 (3.64)	-1.14

†Correlation marginally significant (<.05 *p* >.01)

Table 7.1 T-tests examining relationship between drug of choice and mood/personality questionnaire measures (presented as mean (SD)).

Measure	Total Score	General Descriptive Information	Behaviour Subscale	Cognition Subscale	Emotion Subscale
Mood					
Depression (BDI)	**.456*****	**.409****	**.433****	**.426****	**.396****
Anxiety (STAI)	**.529*****	**.396****	**.545*****	**.434****	**.471*****
Personality					
Impulsivity (BPI)	**.327**†	**.305**†	**.349**†	**.317**†	.239
Disinhibition (SSS)	**.409***	**.299**†	**.402***	**.363**†	**.364**†
Boredom tolerance (SSS)	-.140	-.072	-.083	-.185	-.126
Thrill/Adventure seeking (SSS)	.206	.265	.268	.251	.068
Experience seeking (SSS)	**.311**†	.248	.283	.241	**.322**†
Sensation seeking - total score (SSS)	**.317**†	**.310**†	**.339**†	.291	.249

†Correlation marginally significant ($.01 < p < .05$)
*Correlation is significant at the 0.01 level
**Correlation is significant at the 0.001 level
***Correlation is significant at the 0.0001 level

Table 7.2 Correlations between the MMCQ and mood/personality questionnaire measures.

Factor	Measure	Factor Loadings	Eigenvalue	Total Variance Explained (%)	Cumulative Total Variance (%)
1	Anxiety (STAI)	.918			
	Depression (BDI)	.867			
	MMCQ total score	.682	3.20	40.03	40.03
2	Thrill/Adventure seeking (SSS)	.803			
	Experience seeking (SSS)	.694	1.51	18.92	58.95
3	Boredom tolerance (SSS)	.892			
	Disinhibition (SSS)	.620			
	Impulsivity (BPI)	.551	1.08	13.53	72.48

Table 7.3 Principal components analysis of the mood and craving variables.

CHAPTER EIGHT: DISCUSSION

Findings and Implications

A number of fundamental questions surrounding craving have yet to be resolved; I will attempt to address some of these issues in this chapter, by relating back to the Lateralized Dual-Pathway model and the experimental findings.

An overriding question concerns the development of a suitable biopsychological model of craving. We propose that the Lateralized Dual-Pathway Model helps to resolve some of the controversy surrounding cravings in drug dependence, by positing the existence of two related phenomena governed by different biological mechanisms, with different (but related) phenomenological consequences. I assert that it is the inability to separate these phenomena that has resulted in some of the misunderstanding surrounding the craving concept. I argue that the two processes a) peak at different points in the addictive process, b) are associated with different constellations of affective and cognitive sequelae, and c) may have a different intensity or timecourse for different drugs. As a result, factors such as state of deprivation play a role in the degree to which cravings correlate with other external variables. Moreover, the model presents a testable set of hypotheses for future investigation.

The question of whether cravings are drug-specific or if there is interchangeability between cravings for different substances has also been raised. In this regard, it is of interest to note that craving severity was not a function of drug preference; there were comparable numbers of alcoholics (*n* = 8) and cocaine addicts (*n* = 9) in the severe craving group. Moreover, while it was not surprising that many cocaine abusers had previously experimented with alcohol, at least two of the alcoholics had used cocaine but not become dependent upon it. This observation would seem to argue against a simple availability hypothesis for determinant of drug of choice. Other research has indicated that the majority of heavy cocaine users do not maintain cocaine consumption at its highest levels, instead showing periods of low use or abstinence sometimes lasting months, citing "no desire for cocaine" as an explanation (Cohen, 1990). These questions led us to consider whether personality characteristics, instead, make one vulnerable to cravings for a given drug, as suggested by the self-medication and adaptive models of drug abuse. However we found no relationship between mood/personality variables and one's drug of choice. Hence, questions of how an individual picks his preferred drug, and how dependence on this drug varies over the use cycle, or covaries with use of other drugs, remain unanswered.

As a justification for the use of simple, one-item clinical measures, a number of authors have argued that craving does not require complex measurement. However, a principal components analysis of the 129 question Multidimensional Multitrait Craving Questionnaire (MMCQ) suggests that several factors are implicated in craving. These factors had good face validity, as many were related to known correlates of drug dependence, including negative affect, sensation seeking, and poor self-esteem. Similarly, a "schedule-induced craving" factor emerged, lending credence to the anecdotally cyclical nature of craving, as did craving related to situations of high-stress. Importantly, some of the factors carry behavioural and clinical repercussions. For example, an examination of the factor loadings reveals that distressing cognitions, anxiety, poor self-esteem, and suicidal ideation accounted for nearly a quarter of the total variance observed. This suggests that cravings can be a very disturbing aspect of the addict's abstinence experience, with potentially hazardous consequences. This hypothesis is further supported by strong correlations between craving and questionnaire measures of anxiety and depression. These findings imply that measurement of craving in treatment settings may carry ramifications beyond how the individual copes with abstinence, and also suggest that mood measures may be indicative of relapse risk. This issue requires further empirical validation. This questionnaire was found to have excellent internal consistency and good construct and concurrent validity. Results, therefore, argued against the use of simple one-item visual analogue scales. On the other hand, since "craving intensity" accounted for nearly a quarter of total variance, one-item measures may provide a rough estimate of the individual's state in clinical conditions where time is the chief consideration.

In order to obtain quantitative correlates of craving, we gathered electrophysiological data. We used a variation of Bechara et al.'s (1996) gambling task to index affective and cognitive changes in substance dependence in our ERP investigation, along with measures of behaviour. We saw a direct reduction in amplitudes of the N170-P220 waveform components to high-risk cue stimuli, suggestive of alterations in attention or changes in the attention-getting quality (i.e., salience) of these stimuli. Moreover, these results replicate previous research showing decreased ERP amplitudes in drug addicts *vs.* normal controls (e.g., Biggins et al., 1997; Hada et al., 2000; Hill et al., 1995; Realmuto et al., 1993; Rodriguez Holguin et al., 1999), and extend these findings to dependence severity. However, the research mentioned has typically observed changes in longer latency waveforms, more indicative of alterations in cognitive processing. Decreased N170-P220 amplitudes in this task may also represent an ERP correlate of anticipatory SCRs, as found in the original Bechara et al. (1996) study. As predicted, few significant results were noted in the range of the P3b, which is associated with cognitive processes such as "context updating" (Donchin, 1981; Donchin et al., 1997; Knight and Scabini, 1998; Verleger et al., 1994), or the individual's capacity to process or evaluate stimulus information (Berman et al., 1993; Hill et al., 1995).

In addition, we noted alterations in lateralization associated with craving, with responses to emotionally-charged cues seen mainly over the RH. This supported our contention that addicts depend on the RH for making affective judgments. Extent of lateralization was strongest for positive cues in the low craving group, and for negative cues in the high craving group, suggesting a systematic difference in cue processing. This may suggest attentional bias of individuals with severe cravings towards risky, but potentially rewarding, stimuli. Additionally, we saw decreases in lateralization to reinforcers as a function of craving, suggesting cravings may be associated with deficits in the ability to accurately process affective reinforcement (rewards and penalties).

In terms of the cognitive component of cravings, neuropsychological evidence for frontal lobe involvement was rather weak. However, a MANOVA did lend support to the contention that craving is associated with abnormal lateralization. Clearly, however, the behavioural evidence was more consistent. Cravings appeared to be associated with behavioural activation, at least during the initial phases of novel tasks, paralleling evidence in animal models. This was seen in both the initial block of a reinforcement-based learning task, and when individuals were asked to generate words. Thus, while many cognitive processes appear intact in addiction, behavioural changes in novel situations are evident. Likely, this leads to situations in which the individual's behaviour is not only uncontrolled, but also inexplicable by the individual.

Our findings support the assertion that an understanding of cravings is fundamental to a comprehensive understanding of the addictive process. They support the notion of strong emotional and behavioural constituents in craving, with a relatively weaker cognitive component. The behavioural component appears to consist of behavioural activation and impulsive behaviour, particularly in novel situations. The affective component consists mainly of negative affect, particularly anxiety, but also poor self-esteem, and even suicidal ideation. There is also evidence for both sensation seeking and impulsivity factors in the relationship between mood and craving, which may support the notion of separable dopaminergic and serotonergic brain mechanisms. In general, then, these results provide stronger support for a biologically-based, rather than a psychosocial, model of drug craving. Moreover, these findings carry implications for both prevention and treatment strategies.

Clinical Implications

Given our model, one can expect that dependent individuals have decreased reinforcement-based learning capacities. As such, they likely have difficulty waiting for reinforcement, or dealing with unanticipated contingencies. This suggests that treatment programs aimed at providing immediate reinforcement may be more effective than ones focusing on longer-term outcomes (Petry et al., 1998). In fact, assessment of the addict's ability to delay gratification, or understanding of reward contingencies, may serve as a treatment index. Furthermore, once a client leaves treatment, it is assumed he will be able to generalize his new coping skills to his regular life, apply them to novel situations, and problem-solve in response to unanticipated or anxiety-provoking events (McCrady and Smith, 1986), so generalization of skills in response to novel, unpredictable circumstances must be a treatment focus. If, indeed, stress and anxiety are most likely to initiate relapse, patients should receive particular training in preparing themselves for such situations.

More generally, an understanding of the role of affect in drug dependence is fundamental to treatment success. If dependent individuals have a diminished capacity to experience affect (cf. Gainotti, 1989), then emotional appeals regarding how their actions affect others may offer little incentive. It may be better to give the addict simple rules or direct his attention to inconsistencies between his words and his actions (e.g., "You agreed you would not drink at the party, and then you did"), rather than attempting to induce guilt or urging empathy for others regarding the consequences of his behaviours. Additionally, sharing information with the addict's family or caregiver regarding changes in affective state as a result of drug use may mitigate some of the negative social consequences of the behaviours.

Our model suggests that cravings are associated with both sensation seeking and negative affect, but during different timepoints in the addictive process: Proclivity towards sensation seeking behaviour is associated with active use, while negative affect may play a more important role in abstinence. These observations suggest that individuals with high levels of one or the other may be more amenable to different treatment strategies. Hence, while attempting to substitute drug-taking with novel, stimulating behaviours (Bardo et al., 1996) may be effective with addicts in early withdrawal, strategies for reducing dysphoria and enhancing self-esteem may be more important in later abstinence.

More importantly, the affective patterns common to the addiction cycle should be considered in terms of their possible neurobiological counterparts (in this model, atypical lateralization); there is an understandable tendency to view emotional traits (e.g., excitement preceding use, negative affect in withdrawal, overconfidence preceding relapse, sense of "letting go" during a binge, depression following relapse) as "reasonable responses" to addictive behaviour, rather than as biologically-based symptoms or stages of the disorder. Most of these can be reconceptualized as symptoms characteristic of asymmetric dysregulation, reflecting alternating activation of Gray's (1972) BAS and BIS systems. Moreover, they appear to be somewhat predictable. Such views are in accordance with those of recent studies calling for increased examination of the neural substrates of affective dysregulation as potential therapeutic targets (London et al., 2004).

It has been suggested that clinicians with an incomplete understanding of the neural basis of craving and its correlates may develop unrealistic expectations, and attribute treatment failure to resistance, unwillingness, or denial - attributions not made in other brain injured populations (Gordon et al., 1988). An understanding of craving may help the clinician in a number of ways. Craving severity may provide an index of increased risk of excessive use or negative social consequences (Anton et al., 1995). Information regarding craving intensity may be important in treatment matching, which has been shown to increase compliance rates by as much as 25% in alcoholics (Nielsen et al., 1998); patients who are well matched are more likely to complete treatment, and have better diagnostic outcomes 6 months post-treatment (McLellan et al., 1997). Monitoring of cravings may also help the addict develop a capacity for self-monitoring in general. Mezinskis and co-workers (1998) found measurement of craving to be valuable, as it "encouraged patients to focus on their feelings and discuss them with each other and with their counselors". Exposure to cues in a controlled treatment setting can be used to demonstrate the potential risks of craving-induced relapse, and to act as a positive example of cue resistance (Ehrman et al., 1998). As such, craving measurement may be predictive of future functioning, and may be suggestive of appropriate treatment strategies (Anton and Drobes, 1998; Voris et al., 1991). Finally, given the association of craving with poor self-esteem and suicidal ideation, management of cravings may carry repercussions for self-care.

Implications for Existing Treatment Strategies

Use of a pay-off matrix, in which the client is asked to list and evaluate both the short-term and long-term advantages of their addiction may be helpful in teaching the addict to develop reasonable expectancies (Davis, 1996a), a goal which is crucial for individuals who have a tendency to ignore long-term costs in favour of short-term benefits.

Similarly, our results suggest that daily thought records, in which the individual details potential scenarios with concurrent thoughts and emotions and a description of a rational response (Davis, 1996a), may be effective. This method allows the individual to develop a written record of situations that trigger cravings, and may help in the development of coping skills. It may also counter impulsivity, by introducing a delay between the craving and the behaviour (Davis, 1996a); in a study of impulsivity in gamblers, Castellani and Rugle (1995) suggested that intervention strategies should "focus on helping [individuals] slow down their decision-making process so they can appreciate the potential risks of their behavior". Similarly, Tiffany and Carter (1998) note that that unexpected impediments to automatized behaviour (e.g., mindlessly reaching for an empty cigarette pack) might force the individual to engage in conscious, deliberate behaviour. This method, therefore, introduces a choice point in the addict's behaviour.

Finally, these findings carry repercussions for the Motivational Interviewing Technique (Miller and Rollnick, 1998), which centres around using diagnostic evidence (rather than bullying or coercement) to convince the addict that he has a problem. The general rationale is that the addict does not recognize the excessiveness of his behaviour relative to the norm, so increased objective self-awareness encourages the individual to reduce drug use. It is relatively effective in changing behaviour, with some studies showing individuals twice as likely (59% *vs.* 29%) to attend at least one treatment session (Carroll et al., 2001). This technique relies on quantitative information related to substance abuse. We found relatively few neuropsychological test scores correlated with craving; however, it did correlate with a large number of affective and behavioural measures. The profile (i.e., negative mood, high sensation seeking, and impulsive behaviour in response to novelty) can be presented to the client as a "typical picture" of the dependent individual. At the same time, it may give the clinician insight regarding extent of psychological dependence, without the necessity of asking potentially invasive questions regarding excessive use.

Study Limitations

This investigation had a number of limitations that bear discussion. First, the subject population was comprised exclusively of males over the age of 18, so care must be taken in extrapolating the results to females or to adolescent populations. Further, while the ethnicity of these subjects was not recorded the majority of participants in this study were Caucasian while comparable samples in the United States are typically mainly African American. This may have ramifications to the extent that different nationalities have been shown to have differences in, for example, metabolism of alcohol (e.g., see Hanna, 1978). Thus, the results of this study are primarily generalizable to adult, Caucasian males.

Second, a number of the subjects reported comorbid use of alcohol and cocaine, and many considered themselves recreational marijuana smokers. Almost all were current cigarette smokers. While this finding is not uncommon in studies of substance dependence, the influence of these other substances is clearly unknown. Given the possible number of subclassifications, our obtained *n* would not be sufficient to perform such subanalyses.

Third, the subject population came exclusively from a treatment facility, and most had achieved at least two weeks of sobriety. Future investigations should extend this investigation to other populations, such as current users with differing drug use histories (e.g., experimenters *vs.* long-term users), at-risk populations, or individuals attempting abstinence.

Fourth, previous research in rats has suggested that brain lateralization may have a differential impact on morphine and the psychostimulant drugs (Glick and Hinds, 1985), suggesting results may not generalize to an opiate abusing population.

Finally, individuals who agreed to participate in this study were self-selected, and so may exhibit higher (or lower) than expected levels of craving given the treatment setting.

Summary

Some reviews of craving suggest that motivational and psychological interventions are likely to play the greatest role in decreasing drug use behaviour (Goldsmith, 1998). If this is the case, it is necessary to understand the unique affective and cognitive difficulties of addicts, and how these problems manifest themselves in symptoms of dependence. Our model and experimental research findings point to a number of features which correlate with craving, including deficient reinforcement-based learning, impulsivity in novel situations, increases in negative affect and sensation seeking. We propose that these deficits arise from a common psychobiological origin - increased activation of the left hemisphere.

Knowledge surrounding brain mechanisms of craving and dependence may, eventually, suggest innovative treatment approaches (Cunningham, 1992). Whether or not the concept of craving is ultimately found to have prognostic utility in relapse, clinicians who fail to show concern for the issue may risk reduced client rapport, increased negative affect, or other destructive consequences associated with craving. An understanding of the mechanisms surrounding craving has another benefit: It allows the clinician to reconceptualize negative behaviour on the part of the client as biopsychological rather than motivational in origin. Thus, this greater insight will advance both the understanding of craving as a neural phenomenon, and suggest more effective therapeutic strategies and interventions.

ENDNOTES

[1] This is usually done by means of the "CAGE" questions: Whether the individual has ever tried to *cut down*; whether he feels *annoyed* by criticism regarding his behaviour; whether he feels *guilty* about his behaviour; and whether he uses the chemical as an *eye opener* to help rouse himself in the morning.

[2] A parallel might be using the term "occipital activity resulting from ocular input" rather than "vision".

[3] Note, however, that the notion of drug-induced addiction is not limited to cocaine and heroin; in fact, historically, alcohol (in the 19th century) and marijuana (in the 1920s) had also been targeted.

[4] Although see Matson Cannon and Palmiter (2003) for a description of DA-deficient knock-out mice, who lack tyrosine hydroxylase (TH) in DAergic neurons. These animals resemble wildtype mice at birth, but by 2 weeks "are runted, hypoactive, and hypophagic [and] will starve in the midst of readily available, palatable foods" (Matson Cannon and Palmiter, 2003). In addition, these mice do not engage in nest-building, nor do they reproduce. These behaviours, however, are rescued by L-dopa injections. Speculatively, then, individuals with TH deficiencies may show increased susceptibility to Parkinson's Disease drugs such as L-dopa.

[5] As Gray (1987) chose to put it: "The reason this complication is not apparent in the animal experiments… is straightforward: In animal experiments there is little if any self-selection of environments, this being the experimenter's responsibility, not the rat's".

[6] Tests of Cloninger's model of personality have found that low harm avoidance, which is in part characterized by behavioural activation caused by frustrative non-reward, and high novelty seeking, best predict early-onset alcohol abuse (Otter and Martin, 1996).

[7] Other traits, not of direct relevance to this thesis, have also been shown to correlate with addictive tendencies. These include neuroticism, aggression, non-conformity, and psychoticism. For a review of the many characteristics associated with substance abuse, and particularly alcoholism, the reader is referred to Otter and Martin (1996).

[8] For the sake of completeness, the author notes that Gray (1972) also posited the existence of a third "fight/flight" system responsible for behaviour in response to punishment. However, this system has not been researched in as great of detail (Harmon-Jones and Allen, 1997), is peripheral to a discussion of approach behaviours associated with reward and motivation, and will not be discussed in detail here.

[9] While pressing or depressing a key may not appear to have much ecological validity, Schiff and Bassel (1996) point out that these responses are conceptually similar to grasping and releasing objects. Clearly, these behaviours are much more closely tied to approach and withdrawal.

[10] The authors also note that thinning of the corpus callosum is usually attributed to Marchiafava-Bignami disease, which is relatively rare and characterized by nutritional deficiencies; no symptoms of this disease were present in the group tested, suggesting that thinning is also characteristic of "uncomplicated" chronic alcoholism (Pfefferbaum et al., 1996).

[11] While this was the intent, the factor analysis revealed five questions (marked with an asterisk in Appendix I) with negative loadings, indicating that their interpretation was in the opposite direction of the other questions. For subsequent work with this questionnaire, the author intends to reword these questions as necessary to obtain a consistent pattern of response, as discussed in the text.

[12] While, ideally, one would like to have subject groups who were restricted to use of one substance, most cocaine addicts have also used alcohol. This is not surprising, as alcohol is considered a "gateway drug" for harder drugs. As well, many cocaine users use alcohol in order to "come down" off a cocaine high when necessary. Hence, we used the accepted standard of accepting individuals in treatment for *primary* dependence on either alcohol or cocaine (cf. Killeen and Brady, 2000; McMahon et al, 1999; Patkar et al., 2002; Rosenthal et al., 1990)

[13] This has led some investigators to define control groups in somewhat dubious ways. For example, Stapleton and colleagues (1995) compared polysubstance abusers with a group of control subjects in which "past experimental use of [non-iv] drugs was permitted… but no regular or current use, *except for light use of alcohol and marijuana as well as unlimited tobacco smoking and unlimited consumption of beverages containing caffeine*" (Stapleton et al., 1995, italics added).

[14] At the same time, the authors found a relatively strong correlation (from .36 to .41) between spouses; this correlation was actually *larger* than any of those between genetic relatives. The authors attempted several personality models but, in the end, "could not identify specific observable factors (e.g., personality) in spouses that could have resulted in such a high degree of similarity in a nonobservable trait, such as P300 amplitude" (Hill et al., 1999). The authors posited shared environment, or increased similarities in temperament over time, might explain the findings.

[15] Correlations were run separately for the two groups, as absolute quantities are difficult to equate between alcohol and cocaine.

[16] Visual inspection of grand average data for the groups confirmed that peak amplitudes for both the P220 and the P3b occurred, respectively, at approximately the same latencies in all groups.

[17] For an excellent discussion of problems inherent in the Bonferroni methodology, the reader s referred to Perneger (1998). Particularly useful are his discussions of the danger of Type II errors, problems with the logic underlying Bonferroni correction, and implications for science and medicine should the Bonferroni correction be accepted unquestioningly.

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APPENDIX A: MULTIDIMENSIONAL MULTITRAIT CRAVING QUESTIONNAIRE (MMCQ)

A *craving* is defined as ANY URGE OR DESIRE that is very insistent and difficult to ignore (not just a strong or overwhelming urge).

People can have cravings for drugs, foods, or even behaviours that seem to have addictive qualities. The following questions are designed to learn more about *your* cravings.

The following questions refer to your cravings regarding a given drug or behaviour *in the past two weeks*. Typically, these questions will refer to your *drug of choice.*

If you have experienced cravings for several types of drugs or behaviours over this period and are unsure which one is the topic of this questionnaire, please discuss with the test administrator.

If the behaviour that the question refers to has not happened in the last two weeks, put an *X in the checkbox* marked "Does not apply", but then answer the question based on *imagining what it would have felt like* if it had happened.

If you have any questions, please ask the examiner now.

Dimension Legend:

General Descriptive Information	
Behavioural	
Cognitive	
Emotional	▨

Quality (Subjective)	How overwhelming was your desire for the object of your cravings?
	How obsessive or recurrent were your thoughts about the object of your cravings?
	How compulsive was your use of the substance, or performance of the behaviour?
Intensity	How intense were your cravings?
	How demanding were your thoughts about the object of your cravings?
	How much of a "rush" did you get out of using the object of your cravings?
Quantity	How long did your average craving usually last?
	How much time did you spend thinking about the craved object or behaviour?
	How much time did you spend actively keeping busy, fighting your average craving?
Frequency	How often did you have a craving for the object or behaviour?
	How often did you find yourself thinking about the craved object or behaviour?
	How often did you use the craved substance or perform the craved behaviour?
Other Cravings	How likely were you to have other cravings (e.g., for food, cigarettes, sex, alcohol, or other drugs)?
	How much did you think about these other substances or behaviours?
	How difficult was it to resist these other substances or behaviours?
Responses of Others	How upset or emotional were those around you when you craved the substance or behaviour?
	How much did others try to reason with you when you craved the substance or behaviour?
	How likely were others to avoid spending time with you because of your cravings?
Appetite	How likely were you to crave the substance or behaviour when you felt really hungry?
	How likely were you to crave the substance or behaviour when all you could think about was finding food?
	How likely was searching or looking around for food to lead to cravings?
Energy and Sleep	How likely were you to crave the substance or behaviour when you felt really exhausted?
	How likely were you to crave the substance or behaviour when your thinking was sluggish or disoriented due to lack of sleep?
	How likely was staying up too late or not being able to sleep to lead to cravings?
Eye-opener	How much were cravings first thing in the morning related to improving your mood?
	How much were cravings first thing in the morning related to improving your ability to think or concentrate?
	How likely was the need to wake up quickly to lead to cravings?
Sensation Seeking	How likely was the excitement of an "adrenaline high" to lead to cravings?
	How likely was curiosity about new things to lead to cravings?
	How likely was taking part in risky, exciting activities to lead to cravings?
Risky Relationships	How excited were you by the thought of reaching a "shared high" with friends?
	How likely were you to spend time planning ways in which you could get together with others and use the substance or perform the behaviour?
	How much did others support or encourage you to use the craved substance or behaviour?
Quitting	How powerless did you feel about quitting?
	How much thought did you give to quitting?
	How difficult was it to quit?
Abstinence	How upset did you feel about having to avoid the substance or behaviour?
	How difficult was it to concentrate when you craved the substance or behaviour, but were trying not to?
	How successful were you at not using the substance or performing the behaviour? *

Relapse I ("Letting go" or Bingeing)	How good did relapse feel when it was happening?
	How much did relapse clear your mind of unwanted thoughts?
	How easy was it to start using again?
Relapse II (Recovery)	How guilty did you feel following relapse? *
	How much did thoughts of having to quit all over again occupy your mind after a relapse?
	How difficult was it to stop a relapse episode once it began?
Suicide Risk	How much did your cravings make you feel sad or upset enough to want to end your own life?
	How much did your cravings make you seriously give a lot of thought to ending your own life?
	How likely were your cravings to make you attempt to take your own life?
Automaticity of Processing	How likely were you to be surprised by your cravings for the substance or behaviour?
	How likely were you to find yourself thinking about the substance or behaviour "out of the blue"?
	How likely were you to use the substance or perform the behaviour, without having given it any thought?
Control	How successful were you in suppressing cravings for the substance or behaviour? *
	How well did you resist thoughts about the object of your cravings when you didn't want to think about it? *
	How well were you able to control your use of the substance or behaviour when you made an effort to resist? *
Distractibility	How much did cravings lessen your pleasure in other aspects of your emotional life?
	How much did thoughts about the substance or distract you from other thoughts?
	How much did attempts to use the substance or perform the behaviour get in the way of other things you should have been doing?
Perseveration	How likely were you to find yourself desiring the object or behaviour, over and over?
	How likely were you to find yourself obsessing about the object of your cravings over and over?
	How likely were you to find yourself returning to the source of your cravings, over and over?
Expectations	How much did you crave the substance or behaviour based on expectations of how good it would feel?
	How difficult was it to keep from replaying use of the substance or performance of the behaviour in your mind?
	How difficult was it to avoid habits associated with the substance or behaviour?
Cue Induced Craving	How emotional did you become when something reminded you of the object of your cravings?
	How much did reminders of the object of your cravings make you obsess about it?
	How likely were you to use the object of your cravings when you were reminded of it?
Schedule Induced Craving	How likely were you to get emotional around the time of day you were used to having the object you craved?
	How much was your ability to think clearly affected around the time of day you were used to having the object that you craved?
	How likely were you to give in to your cravings at the time of day you were used to having the object you craved?
Uncertainty	How much doubt or insecurity did you feel when confronted with the object of your cravings?
	How difficult was it to make up your mind about whether or not you wanted the object

	of your cravings?
	How likely were you to check for access or availability to the object of your cravings?
Obsessiveness /Perfectionism	How troubled were you by things being untidy when you were craving the substance or behaviour?
	How much attention did you pay to picky details when you were craving the substance or behaviour?
	How likely were you to spend time putting things in order when you were craving the substance or behaviour?
Vigilance	How likely were to still feel "on your guard", even though you no longer craved the substance or behaviour?
	How much did you continue to think of yourself as "addicted", even when you had been clean for some time?
	How likely were you to behave cautiously in situations where people were using the substance or performing the behaviour?
Impulsivity	How likely was restlessness and a need for the substance or behaviour "right now" to feel overwhelming?
	How likely were you to convince yourself you had to have the substance or perform the behaviour "this minute"?
	How likely was your behaviour toward the object of your cravings to be impulsive?
Ambivalence About Use	How much did cravings make you feel overconfident, then doubtful, about being able to ignore them?
	How likely were arguments with yourself about the pros and cons of using the substance or performing the behaviour to lead to cravings?
	How likely was being put in a position where you could use the substance or perform the behaviour to make you wish you could escape?
Stubbornness	How stubborn did your cravings make you feel?
	How much time did you spend justifying to yourself why it would be okay to use the craved substance or engage in the craved behaviour?
	How much did you use the substance or perform the behaviour behind other people's backs because it was "none of their business"?
Disgust	How likely were you to have cravings when you were feeling disgusted with yourself or others?
	How likely was a preoccupation with details and inadequacies to lead to cravings?
	How likely were attempts to clean, organize, or otherwise "fix" your environment to lead to cravings?
Ambivalence	How likely were you to have cravings when you were feeling resentment towards people you love, or uncomfortable about how nice others were being?
	How likely were doubts about the quality of something you'd accomplished to lead to cravings?
	How likely was doing something you normally enjoyed or thought you'd enjoy, and finding it did not bring you pleasure, to lead to cravings?
Depression	How likely were you to have cravings when you were feeling depressed or sad?
	How likely were thoughts about how slow and difficult it is to get things done to lead to cravings?
	How likely was doing things that made you cry or feel exhausted to lead to cravings?
Suicidality	How likely were you to have cravings when you were feeling worthless and that life was not worth living?
	How likely were plans or daydreams about ways in which to end your life to lead to cravings?
	How likely were suicide attempts to lead to cravings?

Anxiety/ Distress	How likely were you to have cravings when you were feeling anxious, distressed, or uneasy?
	How likely were worries about problems, and thoughts that made your mind race to lead to cravings?
	How likely was doing things that made your heart pound, your palms sweat, or otherwise made you jittery and tense, to lead to cravings?
Boredom	How likely were you to have cravings when you were feeling bored?
	How likely were thoughts about how dull things were to lead to cravings?
	How likely were you to use the substance or perform the behaviour just to have something to do or as a way to keep busy?
Social Anxiety	How likely were you to have cravings when you were feeling uncomfortable or resentful around people?
	How much were cravings brought on by thoughts about having to "fit in" with the crowd?
	How likely were you to use the substance or perform the behaviour because you felt peer pressure?
Camaraderie	How much did wanting to be friendly and have fun with others make you crave the substance or behaviour?
	How likely were thoughts about having a good time with those around you to lead to cravings?
	How likely was seeing friends having a good time indulging in the substance or behaviour to lead to cravings?
Irritability	How likely were you to have cravings when you were feeling annoyed or irritated?
	How likely were thoughts about things that "bugged you" or got on your nerves to lead to cravings?
	How likely was having an argument with someone to lead to cravings?
Fear	How likely were you to have cravings when you were feeling afraid?
	How likely were thoughts about scary things to lead to cravings?
	How likely was doing frightening things to lead to cravings?
Shame/Guilt	How likely were you to have cravings when you were feeling ashamed or guilty?
	How likely were thoughts about things you felt guilty for or should have done to lead to cravings?
	How likely was doing things you knew you shouldn't be to lead to cravings?
Doubt/ Insecurity	How likely were you to have cravings when you were feeling doubtful or insecure?
	How likely was second-guessing your decisions or actions to lead to cravings?
	How likely was trying to do things just to meet other people's standards to lead to cravings?
Paranoia	How likely were you to have cravings when you were feeling distrustful because others were plotting or ganging up against you?
	How likely were suspicions about and preoccupations with others and how they might relate to you to lead to cravings?
	How likely was having to sneak around or be secretive to lead to cravings?
Anhedonia	How likely was a lack of feelings or an inability to enjoy yourself to lead to cravings?
	How likely were thoughts about not feeling as much as you were "supposed" to feel to lead to cravings?
	How likely was taking part in activities that were supposed to be fun or emotional, and feeling little or nothing, to lead to cravings?

APPENDIX B: EVENT-RELATED POTENTIAL TASK INSTRUCTIONS

1. I am going to have you play a game. On the centre of the screen in front of you, you will see five shapes – a square, a circle, a thick line, a triangle, and a diamond – presented one at a time.

2. Each time you see one of these shapes, you have the opportunity to place a bet. You do so by pressing the button on the mouse.

3. After each symbol, you will find out how much you have won or lost (when you press the button) or how much you *would have* won or lost (if you had pressed the button).

   For example: Let's say you see a square, and you hit the button, then you see a 50. That means you won 50 points. If you see a circle, and you hit the button, and then you see a *minus* 100, that means you *lost* 100 points. Then let's suppose you see a triangle, and you *don't* hit the button, and then you see 200. That means you *could* have won 200 points, but you didn't win anything at all, because you didn't hit the button; you didn't place a bet. Do you understand?
   (reiterate as necessary)

4. You are free to decide which shapes to press the button for and which to avoid. You can change your mind at any time, as often as you wish.

5. The goal of the game is to get as many points as possible, or avoid losing points as much as possible.

6. You won't know when the game will end. You must keep playing until the computer stops.

7. All I can tell you is that some shapes are worse than others. You may find all of them bad, but some are worse than the others. You can win if you stay away from the worst shapes.

8. I will start you off at 200 points, but these are just a loan.

9. Occasionally I will stop the game, and ask you how much you think you have won or lost. Then the game will *start over*, and you will be back at 200 points.